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REDUCTION OF UNWARRANTED OPERATIVE INCIDENCE IN OBSTETRICS*

S. A. COSGROVE, M.D., F.A.C.S., JERSEY CITY, N. J.
(From the Margaret Hague Maternity Hospital)

FOR many years emphasis has been placed on the allegedly unnecessarily high maternal mortality in this country. Invidious and condemnatory comparison has been made between this mortality and that of other countries. The conclusion has been repeatedly stated, on the bases of results in many individual clinics, and of various municipal and sectional surveys, that much of it depends on unnecessary and ill-judged operative interference embraced in the American management of obstetrics.

This conclusion, with its direct implication of criticism of the American practitioner, has evidently been accepted very widely by those who aspire to speak for American obstetrics, to judge by the almost numberless articles which have appeared for many years past in our literature. Apparently there was no question that the operative incidence should be reduced.

In regard to the damaging mortality rates alluded to, statistics gathered years ago, some of them by lay organizations with partisan objectives, whose methods of statistical study have been probably justly criticized, are repeatedly published. Yet Runnels[13] in a recent very sane study of this problem, states that the statistics of a decade ago are no longer valid, if they ever were. He shows by unbiased public records that the rate of diminution of maternal mortality in the last ten years has been in excess of the rate of diminution of general mor-

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tality, and mortality in other specific diseases. While no apology is meant or implied for the extent to which women are unnecessarily sacrificed in childbirth all over our country today, it is right that we should recognize that the efforts which our profession particularly, and that of other allied agencies, have put forth to improve conditions, have not been fruitless, and do not warrant a further hopeless outlook.

So, conceding the fact that, in spite of some rather sketchy improvement, mortality rates are still too high, there is practical unanimity in the opinion that both maternal and fetal mortality is in direct proportion to the incidence of operative interference. The actual ratio of incidence of operative interference appears to vary widely.

Barrett[1] quotes from the Woman's Hospital in New York City a total operative incidence of 20 per cent with a gross maternal mortality of 0.46 per cent. He does not appear to include "prophylactic low forceps" in this rather high incidence. Contrasting the mortality in the spontaneous and low forceps groups together, with the mortality in the operative group, the latter is about seven times the former. He says: "Poor results in obstetrics are caused most often by the abuse rather than by the proper use of obstetric surgery." Lynch[7] says that "while there has been a marked increase in the trend toward radicalism in obstetrics, led by some of our trained obstetricians, there is no evidence that the trend toward radicalism has reduced maternal mortality." Fraser and Sparling[3] say the Canadian Government statistics show a mortality rate of 0.23 per cent in spontaneous deliveries as compared to 0.82 per cent in operative or nonspontaneous deliveries. They also point out the increasing trend toward radicalism. Plass[11] quotes the statistics of the State Registrar of Iowa showing almost a 12 per cent operative incidence in all deliveries in that state, with the incidence in the larger cities nearly twice that in the smaller communities. It rises to 23.1 per cent in urban hospitals, which is again nearly twice the rate in rural hospitals. John O. Polak said, "That meddlesome midwifery, with its trauma, infection, and operative risk, adds its quota to the fatalities is beyond question. . . . By increasing the operative incidence in obstetrics, maternal mortalities have been materially raised. . . . The higher the incidence of operative intervention, whether done by the expert or by the novice, the greater the increases of both the maternal and the fetal mortality." Holmes, Mussey and Adair[4] declare that there is an increasing tendency to resort to surgical procedures to assist and complete the delivery of the child and that this surgical intervention, often not indicated, is necessarily associated with a higher mortality among mothers. Jeff Miller[9] stated that other things being equal, the mechanism of a normal labor is still very much better from any angle than any of the improvements we have found for it, and called Nature the best obstetrician of us all, even in cases of definite pelvic contraction. The maternal and fetal results are far better when they deliver spontaneously than the best of surgical skill has been able to achieve. LaVake[5] says an increasing spirit of radicalism has clearly placed the errors and abuses of operative obstetrics in the forefront of those causes that have retarded the reduction of general maternal mortality. He quotes Schauta to the effect that spontaneous birth is by far the best solution of the many complicated problems of contracted pelvis, and that spontaneous birth is in this group of cases much more frequently possible than appears from our statistics.

The New York Academy of Medicine Committee on Public Health Relations,[8] in its report published in 1933, says that perhaps the most prominent feature of the development of modern obstetric practice is in the steady increase in the proportion of operative deliveries and that this tendency is regarded by most observers as one having dangerous potentialities for both mother and child. They found an average operative incidence in 75 per cent of all hospital deliveries in the metropolitan area of 24.3 per cent, and believe that the ratio of deaths following operative deliveries is about five times as great as those following spontaneous deliveries. About half the total maternal deaths followed operative deliveries. The committee reported that in their opinion 76.8 per cent of all the deaths following abnormal delivery

could have been prevented, and that the physician was responsible in 86.8 per cent of all these preventable deaths. They say, "Clearly, a reduction of the mortality rate could be achieved by a reduction in operative interference. . . . If all women who could do so were allowed to deliver themselves spontaneously, and the indications for instrumentation were reduced to those having real validity, . . . there is every reason to believe that there would be a reduction in the deaths."

On the other hand, Lull,[6] while stating that he is in favor of teaching undergraduate students the most conservative type of obstetrics, believes that if a man is at all competent and is delivering all of his patients in a well-equipped modern hospital, it is justifiable to accept a high incidence of operative interference to relieve the woman as much as possible from pains of labor. He acknowledges a total forceps incidence of 45 per cent in full-term deliveries and more than one-third of this forceps interference was for the sole indication of relieving the patient of second stage labor pains. Practically all of this group would have delivered themselves if allowed to continue in labor a few more hours. He says there was no damaging trauma to either mother or child, and claims a gross maternal mortality in the whole group of a thousand cases of only 0.3 per cent.

Several years ago I heard Dr. Norris Vaux quote a moderately high operative incidence for his own clinic and say, I believe not entirely jestingly, that he not only had no apology for his rate of operative incidence but might personally prefer that it had been 100 per cent.

In connection with this whole matter of the relation of operative incidence to gross maternal mortality, one must be very careful not to draw unwarranted conclusions from the statistics. To say that operative mortalities are from 5 to 8 times those of spontaneous deliveries does not justify the superficial inference that if operative deliveries could be entirely eliminated, and all cases be permitted to deliver spontaneously, the general mortality would be reduced to that at present observed in spontaneous deliveries. Higher rates of mortality must necessarily attend the abnormalities which necessitate operative interference. The rates, therefore, which pertain to operative deliveries are susceptible of reduction only to the extent that *misapplied* operative interference can be reduced. The rate for even wholly justifiable and competently performed operative interference will of necessity always be several times higher than the rate for normal, spontaneous delivery.

In relation to the concededly too high operative incidence, most of the published comment places greatest emphasis on the abuse of cesarean section. There is almost unanimous agreement that this operation is too frequently performed; that it is performed for inadequate indications; under improper conditions; in the face of definite contradictions; by many individuals not qualified either to judge of its necessity or to properly perform it.

Newell[10] speaks of the prevalent abuse of one of the most valuable obstetric procedures and says that at the present time cesarean section is so misused that obstetric mortality and morbidity are increased rather than diminished, thus negating appreciation of its true value.

In the sonorous language of Jeff Miller[9] "It is one of the paradoxes and one of the tragedies of medicine that certain measures designed primarily as life saving and health giving, should carry in their abuse, death and invalidism; cesarean section is in this group. Originated for the salvation first of the child and then of the mother, all too frequently it has become a death-dealing agent for them both." He says it is attended by a mortality for the mother ranging from 2 to 25 per cent and

higher, and by a fetal and infant mortality of 15 to 30 per cent. It is by no means the simple and safe procedure it is popularly supposed to be. The mortality of the average operator, and the average mortality of all operators, are much truer indices of the value of a given procedure than are the brilliant results of a single skillful surgeon or single well-organized clinic. Cesarean section by this criterion is clearly a dangerous measure. Obstetrics is still a specialty in itself, not an adjunct of general surgery. The lives of parturient women and of their children are not safe in the hands of men who so regard it.''

Fraser and Sparling[3] state that the principles which should always govern the indications for operation are being lost sight of in the desire to deliver women through the abdomen when and if any abnormality arises. Certain published statistics show, even yet, cesarean section mortalities in certain groups of cases as high as 27 per cent. Schumann[14] reports the average maternal mortality throughout the United States following cesarean section at 5.8 per cent and believes that the indications for the operation have been broadened unwarrantedly. He makes the important point, however, that it is not fair to charge cesarean section with all deaths that follow this operation, irrespective of the primary cause for which the operation may have been employed. For instance, if an eclamptic patient dies after spontaneous vaginal delivery, the death is charged against eclampsia the true cause of death, and not against the method of delivery. If the same woman however, has had a cesarean section, death would be unhesitatingly charged against the type of delivery. He quotes a case in which a uterus was ruptured in an attempted forceps delivery. Cesarean hysterectomy was resorted to in a desperate attempt to save the patient's life. The attempt failed. Death was charged against the cesarean section rather than against the clumsy attempt at forceps delivery which was actually responsible. He says that much more valid information, both as to the value and the abuse of the operation, might be obtained if all statistics were broken down and respective ratios given for the purely elective group of cesarean sections and the necessitous group.

I quite concur with Schumann in this recommendation, and feel sure that such break-down could not fail to be of greatest educational value in teaching the importance of anticipating elective cesarean section by handling cases during any tentative trial of labor with proper reference to this possibility, and the avoidance of section when proper conditions for its performance do not obtain. When performed under suitable conditions, and either by predetermined election, or within a safe period of election, the broadening of the primitive indications for cesarean section is not necessarily so pernicious as some commentators have implied.

Thus Newell[10] admits more than a score of justifiable indications for the operation; Barrett[1] says that their tendency at the Woman's Hospital has been to widen its indications, and that this has not increased either their general mortality rate or their cesarean section mortality; he actually believes that it represents a conservative, rather than a radical, trend; Schumann[14] says: ''It is my opinion, often expressed, that in women with manifest though not necessarily insuperable disproportion, whether this be of maternal or fetal origin, elective cesarean section under local anesthesia, and preferably without a preliminary test of labor, offers the best prognosis for the life and well being of the infant as well as the subsequent health of the mother''; Lull, citing a 10 per cent incidence of section in a series of personal cases, justifies it on the ground that many were referred because of predetermined abnormalities, and says, ''In retrospect of these . . . cases, . . . there were none that I was sorry that I had performed cesarean section upon''; finally, I personally strongly suspect that the gentlemen who are so insistent that perhaps our patients would be better off if we returned to the indications for section of fifty years ago, would most terribly hate to be restricted to those indications in their individual practices.

But while the major furore of discussion thus rages about cesarean section, the improper use of this procedure does not by any means constitute the whole abuse of obstetric operative interference. Polak[12] said some years ago, "As we see it, much of the present day mortality is directly the result of the teachings of some prominent obstetricians who have been busy inventing operative procedures to control the onset of labor, or shorten or eliminate the second stage of labor, or improve the physiological mechanism of placental delivery." He then proceeded to cite induction of labor in all cases at estimated term; the promiscuous use of episiotomy; "elective" version; "prophylactic" forceps; routine manual extraction of the placenta.

The fact that different men will variously estimate the validity of any of these procedures, and the extent of their legitimate application, is beside the point. The important fact is that each of them, like cesarean section, is capable of tremendous abuse, and they are likely, of course, to be abused more widely even than section, because many a man who would not dare essay section would fail to recognize his inability to undertake procedures calling for much greater skill and carrying no less serious and certain risk. The consulting obstetrician encounters most frequently of all situations, perhaps, that in which an attendant, lacking obstetric judgment, impatiently proposes or attempts operations either not properly indicated, or before suitable conditions for their exhibition are fulfilled.

I do not believe that there can be any agreement, even among first rate minds, as to just how high operative incidence should be. Those entitled to be considered leaders in obstetric thought are agreed that a general trend toward conservatism is highly desirable; that nature is capable of delivering babies spontaneously in a surprisingly high proportion of cases; that much operative interference of all kinds, generally practiced, is unnecessary; is employed without sound consideration of proper indications and conditions; and that much of this pernicious interference with nature is based on unworthy motives such as greed, the desire for spectacular notoriety, the selfish conservation of the physician's time and energy. So far as these latter factors affect the issue, such operative interference is wholly bad.

But entire elimination of operative interference, of course, would result in a great and unnecessary increase in maternal and fetal mortality, and in impairment to the health and social usefulness of both mothers and children.

That degree of interference is therefore ideal which will least interfere with the potentially normal processes of nature; which will not per se add artificially to the hazards of mother and child; but which will, on the other hand, tend to reduce to the minimum the hazards, not only immediate, but to future health, of mother and offspring, which perverted or complicated natural processes might without interference entail.

Individual estimation of just what ratio of operative interference will best attain this ideal will present validly wide differences, in relation to the type of thought processes, the experience, and the degree of intelligence and training of different operators. Certain it is that the ideal above defined will be most closely attained when every

case can be decided upon its individual merits by the honest objective judgment of competent men properly trained in the fundamentals of good obstetrics.

Furthermore, no case should ever be decided with one eye on the statistics of the hospital or clinic. I have heard of a clinic wherein forceps incidence was very likely to drop if the maximum total monthly incidence considered allowable for such interference was being approached. This is indeed putting the cart before the horse. Statistics should never be computed in advance. That clinic will render the best service to humanity in which every decision as to interference is based on the best attempt possible to apply honestly good practice standards. If I could be sure that this was true of every case of such interference in my own clinic I should be perfectly happy no matter what the subsequently computed statistics showed.

How may the objectives thus outlined best be attained? All commentators are agreed that the only feasible means for achieving them are embraced in regulation and education. These are both slow processes. Because of this fact they are wholly ineffective unless persisted in with dogged determination, constant effort, repetitious reiteration and infinite patience.

A considerable start in both directions has already been made. Under the heading of regulation, the American College of Surgeons, The American Medical Association, The American Board of Obstetrics and Gynecology and The American Hospital Association have all inaugurated and are carrying forward a more or less well-integrated program. Theirs is the only source of regulatory power, except of course the possibility of direct governmental control. Through the system of approval of the hospitals by the College, the approval for residency and intern training by the Association, the direct and indirect power of these organizations is considerable. But in the very nature of things it is probably too cursory and general to be effective where it is perhaps most needed, that is to say, in the small general hospitals. Even were their scrutiny sufficiently detailed to secure the institution of ideal regulations, the effect thereof must necessarily depend upon the intelligence and spirit with which the regulations themselves are applied.

Regulatory effort, therefore, must be prepared for by a continuous intensive program of education. This program must be manifold. It is necessary to teach:

I. The laity. The program of lay education is well understood, and must impress, among other things: (1) Appreciation of the necessity of prenatal care, including instruction as to the importance of significant symptoms, such as bleeding, and those which evidence developing toxemia. (2) The fact that pregnancy and labor, while ordinarily physiologic, may at any stage become rapidly and dangerously pathologic. (3) That ordinary doctors of conscience and good training are suitable attendants, so long as reproduction remains, in all its phases, physiologic, but that in the presence of abnormalities, the experience, training and judgment of qualified obstetricians is just

as vital to happy outcome, as are the qualifications of the neurosurgeon, the cardiologist, and the ophthalmologist, in their respective fields. (4) That, therefore, the consultative services of obstetricians are just as natural and imperative in obstetric emergencies, as are those of other specialists in the crises of medical and surgical experience. (5) The recompense of the obstetric attendant, both general practitioner and specialist, should be adequate to the attainments, time, and labor which these men employ in the proper management of situations involving the immediate life and death of two-patients-in-one, and the future welfare of both.

II. The profession must be educated. It has been recognized for a long time that undergraduate instruction in obstetrics is deficient in relation to that devoted to other branches. Much progress has been made in this direction, however, within the last two decades, and it is probable that the best of our undergraduate schools today are doing all that they can be expected to do, as to the type of undergraduate instruction, and as to the time allotment devoted to obstetrics in relation to the rest of the curriculum.

The great need in education in obstetrics in this country today is increased opportunity in internship training for the recent graduate, and in similar training for those graduates of longer experience who have not earlier received it. The present facilities for such instruction are all too meager, not only for the manifest demand of physicians of all sorts for it, but for the even more manifest need for it reflected in the statistics of obstetric results which we have already reviewed. This double need may best be met by the cooperation of the management and staff of every hospital, general or otherwise, handling any considerable amount of obstetric material. The means by which such instruction may be undertaken by these hospitals has been discussed in greater detail in an earlier paper.

A by no means negligible, but not so important phase, is the conduct of lecture courses, integrated meeting programs, seminars for practitioners under university and medical society auspices, statewide or local bases. In this connection may be mentioned the helpfulness of hospital conferences open to the profession.

III. Hospital managements must be educated to an appreciation that their contribution to social welfare is not fully met by provision of even a high type of medical, surgical, and obstetric service to their respective communities, but that just so far as they fail to develop all of the educational potentialities which their material represents, they so far fail in their service to society. It is here that the influence of the regulatory agencies will be most significant.

Those who must be responsible for this whole broad program of education are:

I. Government. The Federal Government, both directly, and by collaboration with the State Departments of Health, has already undertaken this responsibility on a broad scale. Its contribution is necessary because of the extent of the program, because only a Fed-

eral agency is capable of properly evaluating and correlating all its phases, and because only the government is able to control funds adequate for its proper fulfillment.

II. The great medical organizations already listed as regulatory agencies, allied groups in the professional field, and many lay groups, which by their altruistic interest have constituted themselves pioneers in this very important field.

All of these have already accomplished so much as to warrant a high degree of satisfaction in, and commendation for, their efforts. But such effort must be persistent and intensified all along the line, in order to achieve the utmost ultimate results.

III. The Obstetrician. The program is closest to the understanding and heart of the obstetrician himself. He must inspire all effort put forth by all of the organizations already mentioned. He must pour into the channels described all his own understanding and his own heartfelt passion for improvement.

But, in arrogating to himself the inspiration and direction of the effort toward betterment of the outlook for parturient American women and their offspring, through education, he must himself be honest in his purpose and approach. He may not say to the general practitioner, "so far must thou go" and then proceed to go himself far beyond the limits which he impresses on others.

He may not preach conservatism to his students and his fellow physicians, but exemplify in his own private practice the most extreme radicalism. He must discipline himself, in the same degree and in the same fashion that he proposes to discipline others, or his own motives and attainment will be discredited and his leadership repudiated.

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THE CLINICAL ASPECTS OF PELVIC ENDOMETRIOSIS*

FRANKLIN L. PAYNE, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania)

THE term endometriosis is applied to a condition peculiar to women, which consists of aberrant adenomatous lesions, possessing histologic and physiologic properties similar to those of the endometrium. Usually the lesions occur in the pelvic cavity to involve one or several of the genital organs or the contiguous pelvic viscera, although the appearance of endometriosis has been reported in the gall bladder, the lungs, and even in the arm.

The well-known proclivity of endometriosis for widespread dissemination is suggestive of malignancy, but its slow growth, limited invasive properties, and dependence upon ovarian stimulation render it a benign process. Despite the limitations of benignity, no other nonmalignant growth is so capable of such widespread involvement as endometriosis. In a study of 307 patients with this condition, a total of 343 major lesions were found, and innumerable minor lesions were present that are not considered in this analysis. The ovaries were the most frequent sites of endometriosis (Table I). Unilateral ovarian involvement constituted 36 per cent of the lesions, and 28 per cent of the growths were bilateral. With 64 per cent of the major lesions of endometriosis located in one or both ovaries, it is obvious that ovarian tissue forms the most fertile soil for endometrial transplants.

TABLE I. LOCATION OF MAJOR LESIONS. (TOTAL NUMBER, 343)

	PER CENT
Ovary:	
Unilateral	36.0
Bilateral	28.0
Cul-de-sac	25.0
Fallopian tubes	3.2
Tubal stumps	1.1
External surface of uterus	2.0
Broad ligament	1.4
Rectovaginal septum	1.1
Umbilicus	1.1
Miscellaneous (cervix, 1; appendix, 1; bladder, 1; laparotomy scar, 1)	1.1

Widespread infiltration of the cul-de-sac formed 25 per cent of the massive lesions in this study. Often this was associated with endometriosis in other situations, particularly the ovaries. At times the process extended into the rectovaginal septum, with the production of a nodular infiltration similar to that of rectal malignancy. Rectal digital and proctoscopic examinations clarify the diagnosis, for endometriosis does not infiltrate the rectal mucous membrane as does malignancy.

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The Fallopian tubes are moderately frequent sites of endometriosis. This site of involvement constituted 3.2 per cent of the pronounced lesions and endometriomas of tubal stumps, usually following salpingectomy or tubal ligation, accounted for 1.1 per cent of them. Other areas of implantation were the external surface of the uterus, the broad ligament, the umbilicus, the cervix, and a laparotomy scar. Umbilical endometriosis is associated with the same condition in other locations as a rule. Three of the four cases in these series were accompanied by cul-de-sac involvement. One case of bladder endometriosis is herein recorded, which was associated with extensive cul-de-sac infiltration. Vesical transplants invade the muscular coats, but do not perforate the mucosal lining of the bladder. The cystoscopic appearance is that of one or more small elevations which vary in color from pale blue to deep purple, depending upon the phase of menstrual activity. They are situated above the inter-ureteric ridge and usually are surrounded by an area of edema but no ulceration is present.

The appendix was the seat of extensive infiltration in one patient. Any portion of the intestinal tract which lies in or near the pelvic cavity may be affected. The most frequent seat is the sigmoid or the rectum. Extensive involvement of the lower bowel may occur, with widespread adhesions, resulting in partial or complete obstruction either from acute adherent angulation or actual impingement upon the lumen of the bowel. The mucous membrane is never infiltrated and rectal bleeding usually is absent to differentiate rectal and sigmoidal endometriosis from malignancy.

ASSOCIATED LESIONS

A characteristic feature of endometriosis is its common association with other pelvic pathology which overshadows both the symptoms and physical findings of the adenomas. Of the 307 patients in this series only 59 (19 per cent) presented endometriosis alone while the remaining 248 patients showed a total of 367 complicating conditions, an average of 1.5 per patient (Table II). Uterine myomas predominated

TABLE II. ASSOCIATED LESIONS. (307 PATIENTS)

	PER CENT
Patients with no allied conditions	59—19
Patients with allied conditions	248—81
Number of complicating lesions	367

Distribution

	PER CENT
Myomas	63.9
Pelvic inflammation	18.7
Uterine retrodisplacement	6.9
Adenomyomas	6.5
Cervical stenosis	0.9
Ovarian cyst	3.3
Ovarian carcinoma	0.6
Umbilical endometriosis	0.9
Tuberculous endometritis	0.6
Bladder involvement	0.3
Fundal carcinoma	0.3
Ectopic pregnancy	0.3

the associated lesions. Sixty-four per cent of the 307 patients with endometriosis had fibroids. Varying forms of adnexal inflammation, usually consisting of peri-

salpingitis or perioophoritis, occurred in 19 per cent of the patients. Endosalpingitis with tubal occlusion was rare and the fimbriated extremities of the tubes generally were open.

Uterine retrodisplacement, because of its obstructive possibilities, is considered to be an active etiologic factor in pelvic endometriosis. Its occurrence in 7 per cent of the patients in this series is suggestive, since it was most common in the younger patients who presented no other likely anatomic cause for the endometriosis.

Uterine adenomyomas, which appeared in 6.5 per cent of the patients, are considered to be manifestations of endometriosis by some authors. They are not so treated in this study, as we believe that they are adenomatous growths which result from endometrial diverticula, and are not true lesions of endometriosis.

The low incidence of cervical stenosis in this series (0.9 per cent) probably does not indicate its true occurrence, for attempts to demonstrate this condition rarely were made in the care of our patients. The occurrence of 12 (4 per cent) ovarian neoplasms, 2 of which were malignant, probably is a coincidence. The possibility of malignant degeneration in ovarian endometriomas has been emphasized. While we might expect endometrial transplants to become malignant with the same frequency that the uterine endometrium does, clinical experience does not justify this expectation. Pelvic endometriosis was associated with umbilical involvement in three instances. No satisfactory explanation of this occurrence has been offered.

AGE DISTRIBUTION

Fundamentally endometriosis is a disease of the menstrual life. The youngest patient in this series was 18 and the oldest 62 years of age. The incidence rapidly increased from 19 per cent in the third decade to 41 per cent in the fourth, with a drop to 37 per cent in the fifth (Table III). More than three-fourths of the patients were between 30 and 50 years old. Two of the cases in the older groups

TABLE III. AGE INCIDENCE. (307 PATIENTS)

	PER CENT
Less than 20 years	0.25
20–30 years	19.0
30–40 years	41.0
40–50 years	37.5
50–60 years	2.0
More than 60 years	0.25

were postmenopausal, probably appearing as hang overs from the menstrual era. The possibility of some extraovarian stimulation must be considered in the light of numerous recent demonstrations of estrogenic activity in the blood and urine after the menopause. Furthermore, it has been suggested that some endometriomas may assume semimalignant characteristics and continue to grow following the withdrawal of ovarian stimulation.

CHIEF COMPLAINTS

The symptoms of endometriosis fall into three general groups: local discomfort, disturbances of genital physiology, and alterations in the function of contiguous viscera. In the present study, dual complaints were the rule. From 307 patients, 596 outstanding complaints were listed, averaging 1.9 symptoms per patient (Table IV). Alteration in the character of the menstrual periods occurred in 56 per cent of the patients, and menstruation was accompanied by extreme pain in 35 per cent of the cases. Intermenstrual discomfort or pain had an incidence of 40 per cent. The descriptions which were applied to this symptom ranged from those of simple lower abdominal discomfort, soreness, or bearing down sensations to attacks of acute pain. These symptoms usually were intensified by the menstrual periods. This also was true of the backache, which occurred in 21 per cent of the patients. The lumbar or sacral areas were the seats of the discomfort which generally was described as a boring pain that became crippling with each menstrual period.

Disturbance in the function of the contiguous organs, chiefly the bladder and rectum, occurred in 17.4 per cent of the patients. The rectal symptoms consisted of pressure, pain, dyschesia, increasing constipation and menstrual diarrhea. Rectal bleeding usually was absent, nor was hematuria a symptom of bladder involvement. The most frequent urinary symptoms were urgency, urinary frequency, and dysuria. Both the rectal and bladder symptoms were definitely increased at catamenia.

TABLE IV. CHIEF COMPLAINTS. (307 PATIENTS)

Total chief complaints	596
	PER CENT
Abnormal menstrual periods	56.0
Intermenstrual discomfort and pain	40.0
Dysmenorrhea	35.0
Backache	21.0
Dysfunction of contiguous organs	17.4
Pelvic tumor	12.5
Marital and fertility difficulties	6.6
Miscellaneous	7.5

Marital and fertility difficulties were present in 6.6 per cent of the cases. These consisted of dyspareunia, infertility, and repeated abortions. Although only 12 patients listed infertility as a chief complaint, it will be shown subsequently that 40 per cent of the married patients had never been pregnant.

The knowledge of a pelvic tumor was listed by 12.5 per cent of the patients as a chief complaint. The majority of these patients had uterine myomas to mask the presence of the accompanying endometriosis.

The miscellaneous complaints consisted of leucorrhea, which was coincidental, and of a menstruating sinus which occurred in four patients, three with umbilical lesions and one with endometriosis of a laparotomy scar.

MENSTRUAL ALTERATIONS

Since alteration in the menstrual periods heads the list of complaints, the identification of a characteristic type of this anomaly would be of diagnostic value. The patients were divided into two groups, those having endometriosis plus other conditions, consisting of 248 patients, and those with uncomplicated endometriosis, numbering 59 patients (Table V). In the former group, 40 per cent had normal periods in contrast to 64 per cent of the latter group who had no menstrual abnormality. This suggests that the menstrual alterations which accompany endometriosis often

TABLE V. MENSTRUAL ALTERATIONS. (307 PATIENTS)

	ENDOMETRIOSIS PLUS ALLIED CONDITIONS 248 PATIENTS PER CENT	ENDOMETRIOSIS ALONE— 59 PATIENTS PER CENT
No alteration	40	64
Abnormal periods	60	46
Abnormalities		
Menorrhagia	61	57
Metrorrhagia	15	14
Menometrorrhagia	16	24
Oligomenorrhea	4.7	5
Amenorrhea	3.3	0

are due to the allied conditions which so frequently accompany it and not to the endometriosis per se. Comparison of the types of menstrual abnormality in the two groups shows little difference, for the various alterations occurred with equal frequency in either class. These figures indicate both the absence of a characteristic

menstrual aberration and the possibility that endometriosis alone often does not cause abnormal menstrual periods. When it does produce alterations, they are dysfunctional in type as the result of disturbed ovarian secretions.

DYSMENORRHEA

Dysmenorrhea, particularly the acquired type, is recognized as being a common symptom of endometriosis and our study confirms this impression. In this analysis, the patients are divided into two groups: those with endometriosis plus allied conditions, 57 in number, and those with endometriosis alone, of which there were 48 (Table VI). In the "endometriosis plus" group, 28 per cent stated that the periods had always been painful with no appreciable recent change. This type of dysmenorrhea ("primary") occurred in only 20 per cent of those with uncomplicated endometriosis. The term "aggravated" is used to denote menstrual pain which began with puberty but subsequently became much more severe. Twenty-five per cent of the "plus group" and 39 per cent of those with no other lesion had such pain. "Acquired" dysmenorrhea was present in 47 per cent of the first group and in 41 per cent of the second. By adding the last two types, we found that newly developed menstrual pain occurred in three out of four patients with endometriosis, either in the form of acquired dysmenorrhea or intensification of a previously existing symptom.

In consideration of the time of the dysmenorrhea, 92 patients had described the relationship between the onset of the pain and the beginning of the period. Since there was no difference between those with endometriosis alone and those with complicating lesions, the groups were combined (Table VII). Intramenstrual pain lasting throughout the period led in frequency with an incidence of 50 per cent. One-fourth of the group had both pre- and intramenstrual dysmenorrhea, while only 18 per cent complained of premenstrual pain, to be relieved at the onset of the flow. Pain which developed during or at the termination of the period to persist for several days occurred in 6 per cent of the patients. These figures suggest that the characteristic time relationship of dysmenorrhea in association with endometriosis consists of its onset prior to the beginning and persistence throughout the duration of the period.

TABLE VI. TYPE OF DYSMENORRHEA

	ENDOMETRIOSIS PLUS ALLIED CONDITIONS	ENDOMETRIOSIS ALONE
NUMBER PATIENTS	57	48
Primary	28 per cent	20 per cent
Aggravated	25 per cent	39 per cent
Acquired	47 per cent	41 per cent

TABLE VII. TIME OF DYSMENORRHEA. (NUMBER OF PATIENTS, 92)

	PER CENT
Premenstrual	18.0
Pre- and intramenstrual	25.0
Intramenstrual	50.0
Intra- and postmenstrual	4.4
Postmenstrual	1.3
Intermenstrual	1.3

STERILITY

In the analysis of the association of endometriosis and infertility, it was found that 40 per cent of the 238 married patients in this series had never been pregnant. The numerous other factors which reduce fertility were not considered nor was the incidence of involuntary sterility determined. Since the occurrence of barren mar-

riages at large is recognized to approximate 12 per cent, it is reasonable to deduce that the patient with endometriosis is three times more likely to be sterile than the average individual.

PREOPERATIVE DIAGNOSIS

With the train of physical changes and functional alterations which accompany endometriosis, its diagnosis would appear to be a simple matter. This is not the case, however, for in a study of 286 patients with endometriosis, the condition was not diagnosed preoperatively in almost two-thirds of the cases (Table VIII). Among the reasons for this failure are the lack of a characteristic symptomatology and of more importance the frequent occurrence of other pelvic lesions which overshadow

TABLE VIII. PREOPERATIVE DIAGNOSIS. (NUMBER OF PATIENTS, 286)

		PER CENT
Correctly diagnosed	104	36
Not correctly diagnosed	182	64
Obscuring conditions		
Myomas		65
Myomas and pelvic inflammatory disease		4
Pelvic inflammatory disease		9
Uterine retrodisplacement		8
Ovarian cyst		6
Ectopic pregnancy		4
Miscellaneous		4

the signs of endometriosis to mask its identity. Among the pelvic conditions which obscured the presence of endometriosis in this study, uterine myomas predominated to account for 69 per cent of the patients in whom endometriosis was not suspected, 4 per cent of which were associated with pelvic inflammatory disease. Simple adnexitis was associated with 9 per cent of the undiagnosed endometriosis, and in 8 per cent of the cases, uterine displacement was not thought to be complicated by endometrial transplants. The presence of benign ovarian neoplasms led the examiner astray in 6 per cent, and in 4 per cent the existence of ectopic pregnancy clouded the pelvic picture. Among the miscellaneous conditions which accounted for 4 per cent of the faulty interpretations were functional dysmenorrhea, dysfunctional bleeding, sterility, and uterine carcinoma.

TREATMENT

Important factors in the choice of treatment are the patient's age, the severity of the symptoms and the removability of the major lesions. With reasonable certainty as to diagnosis in the absence of intolerable symptoms if ovarian involvement or other pelvic pathology does not necessitate treatment, routine observation is feasible and safe. Under such circumstances, the patients are not hospitalized, and they do not enter this statistical analysis. Endometriosis which requires treatment in young patients demands mature surgical judgment with conservatism as the guiding principle. In this study, only 14 per cent of the patients in the third decade were subjected to radical therapy, that is complete ablation of ovarian function, and 36 per cent of those in the fourth decade were treated in this manner (Table IX). The incidence of radical therapy in the older groups increased to 70 per cent where ovarian conservation is less important.

In all age groups, isolated lesions which are readily removable should be treated by extirpation. The presence of widely disseminated invasive growths, which render removal impractical or impossible, necessitates one of two alternatives: surgical intervention or irradiation. Two hundred and eighty-nine of the patients in this series were treated surgically and 15 by irradiation. Complete ovarian

TABLE IX. TREATMENT ACCORDING TO AGE. (304 PATIENTS)

AGE	–20	20-30	30-40	40-50	50-60	60-70
Number of patients	1	56	124	115	7	1
Radical	0%	14%	36%	70%	72%	100%
Conservative	100%	86%	64%	30%	28%	0%

TABLE X. TREATMENT ACCORDING TO THE MAJOR INVOLVEMENT

	NUMBER OF PATIENTS	TREATMENT			
		SURGERY		IRRADIATION	
		RADICAL PER CENT	CONSERVATIVE PER CENT	RADICAL PER CENT	CONSERVATIVE PER CENT
Ovarian	243	51	49	0	0
Cul-de-sac and Rectovaginal septum	47	13	62	15	10
Miscellaneous	14	0	80	14	6

ablation was necessary in 48 per cent of the surgical subjects and in 60 per cent of those who received x-ray or radium therapy.

Since ovarian endometriomas are removable, the preferred treatment for this condition is surgical (Table X). Two hundred and forty-three patients with ovarian endometriosis were operated upon. Bilateral oophorectomy was necessary in 51 per cent, and in 49 per cent, it was possible to conserve one ovary and often the uterus. In young women, for whom conservation of menstrual and procreative functions is so important, unilateral oophorectomy with resection or cautery destruction of transplants, or small endometrial cysts, in the other ovary frequently can be performed. This has been done many times, even in the presence of cul-de-sac transplants, and its importance and feasibility in the surgical treatment of endometriosis cannot be too strongly emphasized.

Endometriosis of the cul-de-sac or rectovaginal septum may be treated by irradiation or by surgery. In the older patients, surgical, or irradiative castration is inevitably curative. For younger patients, with no doubt as to diagnosis, active treatment is indicated only in the presence of definite symptoms. Of the 47 patients in this series who required therapy, three-fourths were treated by surgery and one-fourth by irradiation. The majority of the patients with massive cul-de-sac infiltration who were operated upon received the benefit of conservative procedures. Of those treated by irradiation, the preponderance was given castration doses. The group which received submenopausal doses consisted largely of young women with cul-de-sac transplants who complained of menorrhagia or dysmenorrhea, for whom small doses of intrauterine radium were applied.

The miscellaneous group consists of umbilical, incisional, cervical, vesical, and postsalpingectomy endometriosis. The majority of these patients were young, for whom local excision with ovarian conservation was desirable and practical. Those treated by irradiative castration presented cervical or vesical involvement which necessitated the destruction of ovarian function to insure regression of the lesion.

RESULTS OF TREATMENT

Evaluation of the therapeutic results in endometriosis involves consideration of the following factors: the morbidity and mortality, the unpleasant late postoperative effects, the relief of symptoms, the preservation of genital functions, and the necessity for subsequent therapy. The operative treatment frequently is attended by considerable technical difficulty because of dense adhesions between the lesions and the contiguous pelvic structures. The postoperative morbidity exceeds that following more clean-cut pelvic surgical procedures and an occasional mortality is

inevitable. Of the 289 patients who received surgical treatment for endometriosis, there were two postoperative deaths, an incidence of 0.7 per cent.

The development of unhappy late postoperative reactions follows the lack of ovarian conservation. Our belief in the absolute value of ovarian and whenever possible, menstrual and procreative preservation is too deeply engrained to be modified. Relief of symptoms and regression of the lesions from pelvic endometriosis is assured by total ovarian ablation through the agency of surgery or irradiation. While such therapy is justifiable in the later years of life, in younger women it is to be avoided if possible. Of the 140 patients, in this study, who were treated by radical surgery or irradiation, 49 (28 per cent) complained of severe menopausal symptoms, despite the fact that such procedures were carried out for younger women in a very small percentage of cases. With the modern methods of replacement therapy, many of these patients can be restored to comfort, so far as the flushes are concerned, but the loss of menstrual and procreative functions, of course, is irreparable.

Furthermore, the results of conservatism in the treatment of endometriosis justify its continuation. The 149 conservatively treated patients with adequate follow-up data are divided into three groups: Those with conservation of both uterine and ovarian function, those with preservation only of ovarian function, and a small group with extensive cul-de-sac involvement which is considered separately.

In the first two classes, Group A, with conservation of menstrual function consists of 49 patients, and Group B, with ovarian preservation alone, of 76 patients (Table XI). In Group A, relief of symptoms reached 67 per cent and partial relief 26 per cent, while in Group B complete relief was noted by 93 per cent and

TABLE XI. RESULTS OF TREATMENT, CONSERVATIVE, SURGICAL

	UTERUS AND ONE OR BOTH OVARIES CONSERVED GROUP A	ONE OVARY CONSERVED GROUP B
Number of patients with adequate follow-up	48	76
Relief of chief complaints	67%	93%
Partial relief	26%	5%
No relief	7%	2%
Residual Pain	15%	7%
Dysmenorrhea	23%	0%
Regular periods	79%	14%
Irregular periods	21%	2%
No periods	0%	84%
Pregnancies	10 (21%)	0%
Growth of lesions	7 (15%)	2 (2.6%)
Treatment		
Irradiation	2	0
Surgery	5	2

partial relief by 5 per cent. The incidence of residual pain was twice as great in Group A as in Group B, 15 per cent against 7 per cent. Almost one-fourth of the Group A patients had postoperative dysmenorrhea. In Group A, 15 per cent of the patients required subsequent treatment usually because of increased residual lesions which produced symptoms, while only 3 per cent of the Group B needed further treatment. Thus far, the comparison indicates the desirability of the less conservative procedure, but the next item, subsequent pregnancies, of which there were 10 (21 per cent) in Group A, and, of course, none in Group B, liberally compensates for the higher percentage of postoperative complaints and subsequent treatments in the first group. For young women with endometriosis, surgical conservatism should give way to radicalism only when practice of the former is found to be utterly unfeasible at the operating table.

The therapeutic results in endometriosis of the cul-de-sac and rectovaginal septum are sufficiently interesting to justify separate consideration. Many of the patients in this group presented endometriosis elsewhere, as well as extensive lesions

in the cul-de-sac. Since local excision of the cul-de-sac transplants is impractical, the only means of ablation consists of termination of ovarian function by either irradiation or surgical extirpation. Such a procedure often is not necessary, for the pelvic symptoms frequently arise from the associated pelvic condition and they are relieved by its correction. Consequently, 72 per cent of the patients in this group were treated conservatively and in only 28 per cent was radical therapy necessary (Table XII). Adequate follow-up was obtained upon 43 of the 47 patients. Conservative surgical treatment upon 25 patients resulted in complete symptom relief in 72 per cent and partial relief in 20 per cent. Subsequent pregnancies occurred in 12 per cent to justify the conservative treatment. Study of the behavior of the cul-de-sac lesions showed a decrease in only 19 per cent with no change, or an increase, in 81 per cent. Despite the lack of involution, subsequent treatment was necessary in only 12 per cent to verify the belief that cul-de-sac endometriosis frequently does not produce crippling symptoms.

TABLE XII. ENDOMETRIOSIS OF CUL-DE-SAC AND RECTOVAGINAL SEPTUM.

RESULTS OF TREATMENT (47 PATIENTS)

Radical	13 (28%)
Conservative	34 (72%)

	SURGICAL		IRRADIATION	
	CONSERVATIVE	RADICAL	CONSERVATIVE	RADICAL
Number of patients with adequate follow-up	25	6	5	7
Relief of chief complaints	72%	100%	60%	86%
Partial relief	20%	0%	20%	14%
No relief	8%	0%	20%	0%
Behavior of Lesion				
Decrease	19%	100%	60%	86%
No change	76%	0%	0%	14%
Increase	5%	0%	40%	0%
Unknown				0%
Pregnancies	12%	0%	0%	0%
Subsequent treatment	12%	0%	0%	14%
Irradiation	1	0%	0%	1
Surgery	2	0%	0%	0%

In the irradiation group, which is too small for statistical analysis, 5 were given submenopausal doses and 80 per cent of these were completely or partially relieved of symptoms. Of the 7 patients who received menopausal values, 6 were relieved completely. One, with extensive endometriosis of the rectovaginal septum, did not respond to intrauterine radium, and subsequent destructive doses of roentgen therapy resulted in regression with relief of symptoms.

By considering the patients according to conservative therapeutic procedures, either surgical or irradiative, the results are seen at a glance. In the surgical group, 81 per cent were completely relieved of symptoms, as were 80 per cent of those treated by irradiation. Subsequent treatment was necessary in 8 per cent of the surgical group, but justification is found in 13 (9 per cent) subsequent pregnancies and in freedom from severe menopausal reactions. No subsequent therapy was required in the irradiation group.

SUMMARY AND CONCLUSIONS

Pelvic endometriosis is characterized by the potential multiplicity of its sites of invasion. The majority of the lesions occur in the ovaries and the cul-de-sac, but any of the pelvic structures or the contiguous viscera may be affected.

It is a disease of middle and late menstrual life, with an incidence of approximately 80 per cent between the fourth and sixth decades.

Additional pelvic pathology accompanies endometriosis in four-fifths of the cases to obscure its presence and to cloud the diagnostic picture.

The chief symptoms of endometriosis are those of local pain, alterations in the menstrual and reproductive processes, and dysfunction of the contiguous organs.

The treatment, which may be that of routine observation, surgical intervention, or irradiation, depends upon the severity of the symptoms, the patient's age, and the removability of the major lesions.

Conservatism, particularly in young patients, with preservation of ovarian and, if possible, menstrual and procreative functions is justified by the results: 90 per cent to 95 per cent complete or partial relief of symptoms, 8 per cent necessity for further treatment, and 9 per cent subsequent pregnancies.

133 South 36th Street

FETAL MORTALITY*

William A. Scott, M.D., Toronto, Ont.
(From the Obstetric Service of the Toronto General Hospital)

THE incidence of stillbirths and neonatal deaths has been reduced little, if any, despite the great attention given to this phase of obstetrics during the past twenty years. During the years 1935 to 1937, inclusive, there were 187,165 living births in the Province of Ontario, and during the same period there were 6,162 stillbirths and 5,988 babies died during the first month of life. How to reduce this great loss of life is a question yet unanswered, and it is possible that the study of fetal mortality from the larger centers may provide the material on which sound practice can be based. The present paper is an attempt to analyze the stillbirths and neonatal deaths in the public wards of the Toronto General Hospital for the four years, 1935 to 1938, inclusive. During that time, there were 3,745 deliveries, of which 149 were stillbirths and 80 were neonatal deaths, giving a fetal mortality of 6.1 per cent. This mortality rate has remained at approximately that figure for the last ten years. During these ten years, there have been several changes in our obstetric practice, the principal one being a more conservative attitude regarding the indications for cesarean section, and during the last five years our incidence of cesarean section has dropped from 4.9 to 1.9 per cent of our deliveries. Our attitude regarding heart disease and pregnancy and the treatment of placenta previa has accounted for the biggest part of this drop. In spite of this change in policy, our fetal mortality has remained the same.

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TABLE I. FETAL MORTALITY IN 3,745 DELIVERIES, 1935 TO 1938, INCLUSIVE

Stillbirths		149
A. Before Labor	77	
B. During Labor	72	
Neonatal Deaths		80
		229 6.1%

The causes of these 229 deaths are given in Table II. It is often difficult to be accurate in assigning the essential cause of fetal death, because more than one factor is present in many cases. For instance, toxemia of pregnancy and prematurity, placenta previa and breech delivery, or fetal deformity and long labor occurred in several of our cases, but we have given what we think was the essential reason for the fetal death.

TABLE II. CAUSES OF 229 FETAL DEATHS, 1935 TO 1938, INCLUSIVE

CAUSE	VERTEX	BREECH	SECTION	OTHER PRESENTATIONS	TOTAL
Prematurity	38	8	2	1	49
Fetal deformities	28	5	2	2	37
Cerebral hemorrhage	19	3	1	1	24
Toxemia	17	4	–	–	21
Accidental hemorrhage	17	3	–	–	20
Macerated fetus	13	4	–	–	17
Unknown	12	–	4	1	17
Long labor	9	–	–	1	10
Placenta previa	8	–	–	1	9
Atelectasis	2	1	2	1	6
Prolapse of cord	3	1	–	–	4
Asphyxia	–	2	–	2	4
Icterus gravis	2	–	–	–	2
Craniotomy	1	–	1	–	2
Syphilis	–	1	–	–	1
Diarrhea	1	–	–	–	1
Nephritis	1	–	–	–	1
Pernicious anemia	1	–	–	–	1
Maternal pneumonia	1	–	–	–	1
Ruptured uterus	–	–	–	1	1
Pemphigus	1	–	–	–	1
	174	32	12	11	229

PREMATURITY

It will be seen that prematurity was the commonest cause of death in this series. We have tried to make this figure as accurate as possible, by omitting from that group premature infants in cases of placenta previa, of accidental hemorrhage, and of toxemia of pregnancy where labor was prematurely induced. All public ward patients who are six months or more advanced in pregnancy are admitted to the obstetric wards, and, as a result, there are a considerable number of very small babies included in these figures. Forty of these 49 patients had antenatal care in our own clinic, so the lack of such care was not a great factor, and our results in the care of the premature infant are very satisfactory. In the four years under review, there were 212 infants admitted to the "premature room," weighing under 5 pounds, of whom 28 died. Moreover, 74 of these babies weighed less than 4 pounds, 20 of whom died and 54 went home in good condition. One of these babies weighed 1 pound 15 ounces at birth and was discharged weighing 8 pounds 4 ounces. All babies on our service pass into the care of the Pediatric Service as soon as they enter the nursery, and the credit for the results with our premature infants is due Dr. Alan Brown and his associates.

It is possible that the economic conditions under which public ward patients live may play some part in causing premature labor, for it is our impression that such labors occur more frequently in public than in private practice. A dietary study of public ward patients on relief is being made at the present time, and there is some evidence already accumulated that when undernourished patients are supplied with an adequate diet, the fetus as well as the mother, is benefited, and premature labor is less frequent.

FETAL DEFORMITIES

The second commonest cause of death was deformities incompatible with life, of which there were 37. In some of these, there were additional factors, such as breech, forceps, version, and craniotomy, but obviously the deformity was the essential factor. The study of developmental abnormalities is of considerable academic interest, but its prevention remains a closed book, except where hereditary influence might suggest the advisability of avoiding pregnancy. In this series of 37 deformities, there were 4 cases of accidental hemorrhage, 1 of placenta previa, 9 with hydramnios, 4 of late toxemia, 1 mother had epilepsy, and 1 was in a case of twins, the second child being normal.

TOXEMIA OF PREGNANCY

The late toxemia of pregnancy accounted for 21 deaths. There were 198 cases of toxemia treated in the wards during that time with 45 premature births, of whom 17 died. There were actually 37 stillbirths in this group of 198 cases, but death was assigned to other causes in 16 cases. We do not know how to prevent the toxemia of pregnancy, and pre-eclamptic toxemia plays a large part in fetal mortality. It causes many intrauterine deaths and results in a considerable number of premature births. When this condition develops, the first responsibility of the obstetrician is the life and future well-being of the mother, and the welfare of the child is of secondary importance. In such conditions it is unfair to attribute the fetal death to such things as induction of labor, a breech delivery, a long labor, or cesarean section. The early toxemias cause little danger to the fetus except in those few cases where therapeutic abortion becomes necessary. In the four years under review, there were 132 cases of vomiting of pregnancy treated in the wards, and in 9 of these the pregnancy was terminated.

SYPHILIS

The influence of syphilis as a determining factor in fetal and neonatal deaths has almost disappeared in this clinic. Only 1 death in this series was due to syphilis and that was in a patient who had been under intensive treatment for some considerable time before pregnancy, but in whom a negative Wassermann could not be obtained. It was a breech delivery, but syphilis accounted for the fetal death. In 2,904 Wassermann tests on obstetric patients, there were only 29 positive results, and for ten years only about 1 per cent of our obstetric patients have had positive Wassermann reactions.

BREECH DELIVERY

Breech deliveries resulted in 32 of our deaths, and Table III is an analysis of these cases.

It will be noted that in these 32 breech cases, breech extraction is listed as having been performed 12 times. By breech extraction is meant those cases in which some operative manipulation was carried out; in the other 20 cases there was no manipulation except for episiotomy and pressure on the fundus. Only the last 7 of these deaths could be attributed to the breech delivery. The 3 cases of cerebral hemorrhage all followed breech extraction, the babies weighing 9 pounds, 9 pounds, and 4 pounds 10 ounces, respectively. Only 1 of the three was a primipara, and it was the only case of cerebral hemorrhage in which the diagnosis was confirmed at autopsy.

TABLE III. FETAL MORTALITY IN BREECH DELIVERIES

STILLBIRTHS 25, NEONATAL DEATHS 7, TOTAL 32	
Spontaneous Delivery 20, Breech Extraction 12	
CAUSE OF DEATH	
Prematurity	8
Fetal deformity	5
Macerated fetus	4
Toxemia of pregnancy	4
Accidental hemorrhage	3
Syphilis	1
Cerebral hemorrhage	3
Asphyxia	2
Atelectasis	1
Prolapse of cord	1
	32

External version is attempted on breech cases whenever feasible, but it is often impossible to accomplish, and in others the condition recurs after the baby has been turned. It is our belief that cesarean section in the interest of the baby, in breech cases, is rarely indicated, although we realize that however skillful the obstetrician, the fetal mortality in breech deliveries will always be higher than in vertex presentations. An exaggerated idea of the value of the infant's life compared to increased danger to the mother has been one factor in the great increase in cesarean section. It is probably true, in general, that where the maternal death rate is high, the fetal mortality will also be high, which is indicative of the fact that conservative obstetric practice is safest for mother and child. Nevertheless, in some centers there is a relatively high maternal mortality and a relatively low fetal death rate. In such instances there is a question whether an additional risk has not been placed upon the mother in the interest of the child. We have come to realize that breech delivery with the premature child requires greater skill in many instances than with the mature baby. The diameter of the head in a premature child is greater than the hips, and the child's body may slip through the cervix before the latter is completely dilated. We have now made it a rule that a staff member must be present at breech deliveries in all cases of premature labor.

PROLONGED LABOR

Prolonged labor was the cause of death in 10 cases. Of these, 9 were vertex presentations and one was a brow. Six of the vertex cases were occipitoanterior positions, 1 was R.O.T., 1 was L.O.P., and 1 was R.O.P. In our experience, therefore, occipitoposterior position is not an important cause of fetal death, and a long first stage is usually due to the cervix rather than to the position of the head. Of these 229 fetal deaths, 7 occurred in persistent occipitoposterior positions, 3 of whom had spontaneous deliveries. One occiput posterior was in a patient with eclampsia, in whom labor lasted seventy-seven hours, and 1 was in a patient with accidental hemorrhage in whom labor lasted fourteen hours. It cannot be denied that prolonged labor jeopardizes the life of the baby, but attempts to shorten such labors, except by cesarean section, carry an even greater danger to the child's life as well as increasing the maternal risk. The problem of the slowly dilating cervix is yet unsolved, but the conservative obstetrician does not feel that cesarean section is the proper solution.

CESAREAN SECTION

There were 12 deaths following cesarean section, of which 6 were stillbirths and 6 were neonatal deaths. These are tabulated in Table IV.

It will be seen that there were 4 fetal deaths from unknown causes in patients delivered by cesarean section, and in 2 of these the section was done for dis-

TABLE IV. FETAL DEATHS IN CESAREAN SECTION, 1935 TO 1938, INCLUSIVE

CAUSE OF DEATH		INDICATION FOR SECTION	
Unknown	4	Contracted pelvis	5
Deformities	2	Accidental hemorrhage	3
Atelectasis	2	Ruptured uterus	2
Prematurity	2	Placenta previa	1
Cerebral hemorrhage	1	Carcinomatosis	1
Ruptured uterus	1		

proportion as operations of election, 1 patient being a repeat section done before labor began. The case with cerebral hemorrhage was done early in labor, and at autopsy there were also found petechial hemorrhages in the pleura and the abdominal cavity. It was probably a case of hemorrhagic diathesis occurring before labor. If we eliminate these cases where section was done for accidental hemorrhage, placenta previa, and ruptured uterus, we still find 6 fetal deaths following cesarean section in this series, which is an indication that abdominal delivery by no means guarantees the life of the baby.

ABNORMAL PRESENTATIONS OTHER THAN BREECH

Table V is a summary of fetal deaths in cases of abnormal presentation, other than breech. In this group there were 7 stillbirths and 4 neonatal deaths. In Table V, the cause of death occurs opposite the type of delivery.

TABLE V. ABNORMAL PRESENTATIONS, 1935 TO 1938

PRESENTATIONS		DELIVERY	CAUSE OF DEATH	
Face	6	1 Spontaneous	Deformity	1
		2 Forceps	Asphyxia	1
			Atelectasis	1
		3 Version	Long Labor	1
			Placenta previa	1
			Unknown	1
Transverse	3	2 Version	Ruptured uterus	1
			Asphyxia	1
		1 Embryotomy	Deformity	1
Brow	2	2 Forceps	Cerebral hemorrhage	1
			Prematurity	1

It will be noted that in these 11 cases causes other than the presentation accounted for 5 of the fetal deaths; namely, deformity 2, placenta previa 1, ruptured uterus 1, and prematurity 1. The 3 patients with transverse presentations entered the hospital after having been in labor for some considerable time. Face, brow, and transverse presentations present difficult obstetric problems, and the operative procedure necessary will result in death of some babies. Each case is a problem in itself, and in many instances the life of the mother is the immediate concern of the obstetrician. Any analysis of fetal mortality in which fetal deaths are tabulated as due to the method of the delivery, without consideration of the indications, is fallacious. The mere fact that many stillbirths occur after operative delivery does not necessarily mean that this method of treatment was incorrect, since operative intervention is obviously more frequent in complicated cases. It is true that infant mortality is great following high forceps delivery, yet the only alternative in most of these cases is version and extraction, where the fetal death rate will be equally high.

FORCEPS DELIVERY

It is obvious that where forceps delivery is practiced only upon definite indications, the infant mortality will be higher than where the so-called "prophylactic" forceps operation is done. If we eliminate prophylactic forceps, all analyses of

fetal deaths will show that twice as many follow operative as follow normal delivery. Nevertheless, failure to do a forceps delivery when there is delay in the second stage subjects the child to even greater danger. We have the feeling that certainly one, and possibly two, of the fetal deaths in this series might have been avoided had forceps been applied somewhat earlier. Skill in the application of the forceps and in the subsequent delivery lessens the chance of injury to the baby. The frequent mistake of a young operator is the rapidity with which he delivers after having made his forceps application. There were 28 cases in which fetal death followed forceps delivery. Of these, 24 were vertex presentations, 2 were face presentations, and 2 presented as brow.

ANTE-PARTUM HEMORRHAGE

There were 29 fetal deaths in which the mother suffered from ante-partum hemorrhage, 20 of these being accidental hemorrhage and 9 of them placenta previa. In these cases the life of the mother is the prime consideration. In severe cases of accidental hemorrhage, the child is practically always dead and unless routine section is done, about 25 per cent of the children will not survive, and even if section is done, the fetal mortality will still be high. In occasional cases, the welfare of the baby is the determining factor in the method of treatment, but such cases are rare in this clinic where we have no routine method of treating placenta previa, but attempt to use that method which we feel is most applicable to the given case.

CEREBRAL HEMORRHAGE

Table VI is an analysis of all the cases of cerebral hemorrhage of which there were 23.

TABLE VI. CEREBRAL HEMORRHAGE, 1935 TO 1938

PRESENTATION		DELIVERY	
Vertex	19	Spontaneous	10
		Forceps	7
		Version	2
Breech	3	Extraction	3
Transverse	1	Version	1
	23		23

Of these 23 deaths, 13 were stillbirths and 10 were neonatal deaths. The diagnosis was confirmed by autopsy in 12 cases, and in the other 11 there was either a clinical diagnosis alone or a clinical diagnosis substantiated by a spinal puncture. It is interesting to note that of these 23 cases, 19 were vertex presentations and 10 of them followed spontaneous delivery. However, this does not mean that these were easy normal labors, although some were in that category. Others were hard labors with prolonged first stage, and although the loss of fetal life is regrettable in these cases, yet we feel that cesarean section was not indicated, and we are also of the opinion that any attempt at delivery per vaginam before the cervix was dilated would not have decreased the danger to the child. There is the occasional case of labor in a primipara with a slowly dilating cervix, where section may be indicated in the interest of the child, but in our practice such cases are few in number.

SUMMARY

1. In this analysis of 229 fetal and neonatal deaths during the last four years, an attempt has been made to evaluate factors responsible for the infant mortality.

2. A reduction of fetal mortality is highly desirable, but care must be taken that efforts to reduce the number of fetal deaths do not lead to radical measures endangering the mother.

3. Prematurity has been the commonest cause of fetal mortality in our experience. The incidence of premature labors may be reduced to some slight extent by prenatal care, but the care of the premature baby offers the greatest hope of reducing this cause of fetal death.

4. Complications of pregnancy and labor inevitably increase the danger to the baby as well as to the mother. In the management of such complications, the wise obstetrician is mostly concerned with a correct obstetric judgment.

5. In obstetric complications, skill in judgment is often of more importance than technical dexterity, but this is more difficult to acquire.

ASPHYXIA OF THE FETUS AND THE NEWBORN INFANT*

A Study of the Clinical and Pathologic Changes Produced by Intrauterine Asphyxia Due to Placenta Previa and a Consideration of Methods to Prevent or Minimize Fetal Anoxemia

Stewart H. Clifford, M.D., Boston, Mass.

(From the Boston Lying-in Hospital, the Departments of Obstetrics and Pediatrics of the Harvard Medical School and the Department of Child Hygiene of the Harvard School of Public Health)

INTRAUTERINE asphyxia is known to produce physiologic and pathologic changes involving every organ and tissue in the body. It is the cause of a vast number of fetal deaths and is responsible for much of the morbidity and mortality encountered in both premature and full-term infants. Fetal asphyxia is being mentioned increasingly as an important etiologic factor in many neurologic conditions encountered in older age groups.

There are many important aspects of this condition that should receive more careful study. Much can be accomplished along obstetric lines to minimize the effects of unavoidable intrauterine asphyxia in some patients and to prevent the occurrence of fetal asphyxia in others. It is suggested that when advances are made in the prevention and management of fetal asphyxia the reward will be a significant drop in fetal and neonatal mortality and morbidity.

Intrauterine asphyxia is ordinarily considered with relation to its effect on isolated organs or tissues, such as the lungs or brain; or in its relation to isolated diagnoses, such as asphyxia neonatorum or atelectasis. At the present time evidence is being accumulated to show that intrauterine asphyxia should be considered as affecting every organ and tissue in the body to a varying and unpredictable degree.

*Presented at the First American Congress on Obstetrics and Gynecology, Cleveland, Ohio, September 11 to 15, 1939.

SUMMARY OF THE CLINICAL FINDINGS FOLLOWING INTRAUTERINE ASPHYXIA DUE TO PLACENTA PREVIA

The clinical and post-mortem findings associated with fetal asphyxia due to hemorrhage from placenta previa have been studied in 11 infants, all delivered by cesarean section prior to the onset of labor. It is of practical importance that in this series of fatal cases the asphyxia accompanying partial interference with placental circulation produced no significant alteration of the fetal heart and in no instance was meconium passed. This, in spite of the fact that 8 of the 11 infants required resuscitation at birth while one other, not recorded as requiring resuscitation, was cyanotic and in poor condition from birth.

Six of the 11 infants were in poor condition from birth and lived from four to thirty-six hours. They exhibited respiratory distress with labored, grunting breathing, dilatation of the alae nasi and marked retraction of the costal margins. They were subject to varying degrees of cyanosis; their cries were feeble, their reflexes were absent and their muscles hypotonic. The majority showed petechial hemorrhages and subcutaneous ecchymosis. One vomited blood while 2 developed tense and bulging anterior fontanels, later shown to be due to a marked accumulation of clear cerebrospinal fluid.

Three infants were considered to be in fair condition for several hours following their resuscitation at birth, except for labored respirations and cyanosis of the extremities. Severe respiratory embarrassment then developed, accompanied by retraction of the costal margins and recurring attacks of generalized cyanosis. One infant developed petechial hemorrhages in the skin and scleroderma; one became spastic and had convulsive twitchings while the third developed melena and bled from the nose. They died between the ages of 6 and 36 hours.

The remaining two infants breathed spontaneously at birth and were considered to be normal for several hours. They then developed the same syndrome of respiratory distress characteristic of the rest of the group. One infant bled from the nose and mouth and into the subcutaneous tissue of the thorax before his death at twelve hours. The second infant developed labored respirations at two hours of age; at seventeen hours the respiratory distress was marked and the anterior fontanel became full; at 3 days the fontanel became tense, and apnea, cyanosis, scleremia, and generalized muscular rigidity developed. Lumbar puncture produced a bloody cerebrospinal fluid containing 50 per cent crenated red blood cells per cubic millimeter. The baby died at the age of six days. Among other findings the autopsy showed hemorrhage in the subarachnoid space and into the ventricles as well as an extreme degree of encephalomalacia.

SUMMARY OF THE PATHOLOGIC FINDINGS FOLLOWING INTRAUTERINE ASPHYXIA DUE TO PLACENTA PREVIA

Interference with placental circulation as the result of hemorrhage from placenta previa apparently produces in the fetus an initial state of intense blood vessel congestion that may be followed by the liberation of edema fluid, hemorrhage, and even tissue necrosis. The phase of blood vessel congestion involves all organs and tissues and extends to the finest capillaries. This stasis and pooling is largely responsible for the observed increase in weight of the lungs, the liver, and the heart and for the less marked increased weight noted for the brain, the spleen, the kidney, and the thymus.

The second stage is characterized by the liberation of edema fluid into the tissue spaces, the tissues and the body cavities. This edema

fluid may be observed in the subcutaneous tissues, in the muscles of the extremities and the heart, in the periadrenal, the peripancreatic and the retroperitoneal tissue. It may be seen in the capsule or stroma of the adrenals, the thymus, the liver, and the pancreas. Edema of the pleura, the lung stroma or parenchyma and the brain may be observed. The peritoneal, the pleural, and the pericardial cavities may show considerable free fluid, while the subarachnoid space shows an increased amount of cerebrospinal fluid. The accumulation of edema fluid contributes to the increased weight observed in the various organs.

In the third stage there is the liberation of smaller or larger numbers of red blood cells either through diapedesis or actual rupture of small vessels. The hemorrhage may be of the petechial variety and be found scattered through the various organs to a greater or less degree. The hemorrhage may be more extensive and be found in the parenchyma of the lungs, the liver, and in the intestinal tract. Alveolar hemorrhage may occur, ranging from occasional areas of extravasated blood to true alveolar hemorrhage. The cerebrospinal fluid may contain a small amount of microscopic blood, slight gross blood staining, or a large amount of free blood. The brain itself may show scattered petechial hemorrhages or at times a large accumulation of blood in the ventricles.

In the fourth stage evidence of actual tissue necrosis may be found. The liver seems particularly susceptible and shows fatty infiltration of varying degree or a marked necrosis and dissolution of tissue accompanied by hemorrhage. The brain may show changes ranging from areas of ganglion cell degeneration to widespread encephalomalacia.

The clinical manifestations encountered depend on the degree and extent of the underlying pathologic changes. The central nervous system changes account for the difficulty in resuscitation, the alteration in respiratory rate and rhythm, the loss of muscle tone and the development of convulsive movements. The congestion, edema and hemorrhage, seen generally in the various organs, when occurring in the lungs render them incapable of normal expansion and result in massive atelectasis with its attending clinical manifestations. With only the anterior margins and a few central lobules of the lungs expanded, normal oxygenation of the newborn's blood is impossible; anoxemia after birth is therefore substituted for the preceding interference with fetal circulation. The extrauterine anoxemia may well be of greater severity than the initiating fetal process and be largely responsible for the progressive fatal development.

An appreciation of the widespread pathologic changes that may be produced by asphyxia is of great practical help in the diagnosis and treatment of abnormal symptoms as they appear in the newborn.

THE CONTROL OR PREVENTION OF FETAL ASPHYXIA

The harmful effects of intrauterine asphyxia on the fetus and newborn infant are so real that normal labor should be managed in such a way as to keep this asphyxia at a minimum or, if possible, to prevent

it altogether. Judicious choice of anesthetics and their skilled administration will prevent injurious fetal asphyxia occurring in many cases.

Nitrous oxide and oxygen is widely used, both as an anesthetic and as an analgesic agent. Every anesthetist so using it in pregnancy should be familiar with Eastman's conclusions: "Nitrous oxide mixtures, administered to mothers in proportions of 85:15 or weaker, and for periods of less than five minutes, regularly cause moderate degrees of fetal anoxemia, but the normal, full-term infant is apparently not harmed. When nitrous oxide is given in concentrations of 90:10 or stronger, over periods which exceed five minutes, marked degrees of fetal anoxemia are produced in about one baby out of three and occasionally profound asphyxia neonatorum results."

Other methods of obtaining obstetric anesthesia or analgesia must be appraised not only from the point of view of their effect on the mother, but also as to their possible effects on the fetus. At first consideration spinal anesthesia should be particularly satisfactory for the fetus, but in practice the fall in maternal blood pressure that occasionally occurs has produced most severe fetal asphyxia. Theoretically cyclopropane would seem to be ideal for the fetus because of the high oxygen content in the anesthetic mixture. In practice there is reason to believe that it also is responsible for severe fetal asphyxia (C. A. Smith), due to the fact that it produces such marked capillary dilatation that the venous and arterial blood are practically indistinguishable. The blood circulates through the capillary bed of the placenta so rapidly that the fetus fails to receive an adequate oxygen supply.

In an earlier communication, a mortality of 54 per cent was reported from this hospital for infants weighing 5 pounds or less when delivered by cesarean section. At that time it was pointed out that cesarean section theoretically should have been the safest method for the delivery of a premature infant, since it eliminated the factor of traumatic injury. It was suggested, however, that the unexpectedly high mortality might have been due to the substitution of an even greater fetal hazard, asphyxia, for that of trauma. The intrauterine asphyxia was felt to be at times the result of the method of anesthesia employed.

Since that time methods of anesthesia have been sought that would permit satisfactory maternal anesthesia without producing harmful fetal asphyxia. The most successful methods thus far encountered are local anesthesia and rapid nitrous oxide-oxygen-ether anesthesia. The local anesthesia technique is time consuming and requires great cooperation on the part of the patient. Under the rapid method of anesthesia the mother usually receives no preliminary medication and is brought to the operating room completely conscious; she is then scrubbed and draped; the operating team stands by, scrubbed and ready to begin the operation; all these preparations being completed, anesthesia is then induced. Surgical anesthesia is produced as rapidly as possible and the section performed. The time elapsed from the start

of anesthesia to the delivery of the infant is usually about four minutes and this interval is so brief that no signs of fetal asphyxia are produced. When a longer period of anesthesia is required for delivery, great care must be exercised to keep the oxygen content above 15 per cent; complete relaxation is obtained by adding ether to the mixture. The lapsed time from induction of anesthesia to delivery must be kept as short as consistent with safety. That these principles are sound is attested by the fact that in the past two and one-half years there have been 24 infants weighing less than 5 pounds delivered by cesarean section in this hospital with a gross infant mortality of 16.5 per cent.

Asphyxia may produce sufficient injury to the respiratory center to delay or prevent the normal development of extrauterine breathing. Morphine and excessive ether administration likewise may inhibit the respiratory center of the fetus. In this hospital no opium derivative is administered to a mother within four hours of the anticipated birth of her child except under rare circumstances. The anesthetists strive to keep the total amount of ether administered during any delivery at an absolute minimum. The barbiturates result in sleepy babies, and although we have observed no ill effects from their use in normal full-term deliveries, we discourage their use in premature deliveries as being a possible and unnecessary hazard.

The practice of abnormally prolonging the second stage of labor by pressure on the perineum accompanied by general anesthesia, should be discouraged as it may produce a serious degree of fetal asphyxia. I am indebted to Dr. Frederic Schreiber for permission to report an illustrative case.

A baby was seen when fifteen hours old because of convulsions and constant twitching of all extremities. The color was good but the respirations were grunting. All extremities were spastic and the eyes were held to the right in spasms. The story obtained was that the child's head had been held back and nitrous oxide given for one-half hour until the arrival of the attending physician. The baby was born spontaneously as soon as perineal pressure was released and anesthesia discontinued. The appearance was that of asphyxia pallida; the baby began breathing only after fifteen minutes of resuscitation. The baby died after forty-eight hours. There was no gross intracranial hemorrhage. All the organs showed the changes associated with asphyxia as already described in this paper. Dr. Gabriel Steiner described the microscopic sections of the brain. Two devastation areas associated with asphyxia were found in the region of the X nucleus in the medulla, on the right side, probably responsible for the infant's death. There were extensive changes, secondary to asphyxia, in the frontal and motor cortex. Had this child lived, it could be expected to show spasticity, convulsions, or mental retardation, depending on the location and extent of the lesions.

Conversely, *if the cervix is fully dilated*, shortening of the second stage of labor by low forceps delivery and episiotomy can reasonably be expected to reduce the incidence and degree of fetal asphyxia.

Careful study of the complications of pregnancy that are each potential causes of fetal asphyxia may result in methods of obstetric management equally beneficial to mother and child. Irving's contribution to the management of placenta previa is an example of such an approach.

Irving studied 308 cases of placenta previa equally divided into three chronologic groups, with each group representing a different method of obstetric management. The method of treatment employed was found to exert a marked influence on both the maternal and net fetal and neonatal mortality as shown in Table I. The

TABLE I. THE INFLUENCE OF THE METHOD OF MANAGING PLACENTA PREVIA ON THE MATERNAL, FETAL, AND NEONATAL MORTALITY

	CASES	BAGGING	A. F.†	B. H. V.†	E. T.†	C. S.†	M. M.†	NET FETAL AND NEONATAL MORT.*
		%	%	%	%	%	%	%
1916-23	105	44.8	32.4	1.0	1.0	2.9	7.6	47.0
1924-29	103	40.8	3.9	24.3	1.1	21.4	11.6	31.1
1930-34	100	16.0	0.0	23.0	6.0	56.0	2.0	20.3

*Infants weighing less than 4 pounds, those dead on admission, and those with gross malformations are excluded.

†A.F., accouchement forcé; B.H.V., Braxton Hicks' version; E.T., expectant treatment; C.S., cesarean section; M.M., maternal mortality.

successful plan of treatment was as follows: Patients revealing no evidence of uterine infections with infants thought to have a good chance of survival were all delivered by cesarean section; similar patients with dead infants, with infants estimated to weigh less than 4 pounds or with infants grossly malformed at x-ray examination, were all delivered by Braxton Hicks version or by using the Voorhees' bag. Infected patients were delivered by cesarean section followed by hysterectomy with drainage, whatever the fetal condition. This plan of treating placental previa not only resulted in a reduction of net fetal and neonatal mortality from 47 to 20 per cent, but also in a reduction of maternal mortality from 12 to 2 per cent.

CONCLUSIONS

Intrauterine asphyxia produces fetal damage proportional to the degree and duration of the anoxemia and to the susceptibility of the individual fetus.

A hypothetical explanation of the physiology of asphyxial injury is presented. As the result of asphyxia every organ and tissue of the fetus is subjected to a varying degree of vascular congestion; with further continuation of the asphyxia, every organ and tissue may develop a varying degree of edema, hemorrhage, and cell injury. The resulting clinical manifestations are dependent on the degree and extent of the underlying pathologic changes.

The prevention of fetal asphyxia demands methods of obstetric anesthesia and analgesia that do not produce fetal anoxemia or injure the fetal respiratory center.

The practice of holding the head back and abnormally prolonging the second stage of labor may produce a dangerous degree of fetal asphyxia and should be abolished. Efforts should be made to shorten the second stage when conditions are favorable.

A varying amount of fetal anoxemia is an unavoidable part of certain complications of pregnancy. The ideal method of obstetric management under those conditions represents a different individual problem for each complication. In general, a method of treatment will be sought that will minimize the degree and duration of the intrauterine

asphyxia, yet at the same time safeguard the mother's welfare. In the case of intrauterine asphyxia, resulting from placenta previa, such a study has produced a plan of treatment beneficial to both mother and child.

The prevention of intrauterine asphyxia or the minimizing of its effects when unavoidably present should result in a real reduction in fetal and neonatal morbidity and mortality.

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1101 Beacon Street

THE CONTROL OF CANCER IN WOMEN FROM THE MEDICAL VIEWPOINT*

With Special Reference to the Schiller Test and the Colposcope

Raymond E. Watkins, M.D., Portland, Ore.

(From the Department of Obstetrics and Gynecology, University of Oregon School of Medicine)

CANCER is the second most frequent cause of death in this country. It has risen from tenth place to its present position in the short space of thirty years. Only heart disease now exceeds it. In women death from cancer of the female genital organs is steadily increasing, in spite of all our efforts to control it. There was a mortality of 16,442 in 1930, with yearly increase to 19,198 in 1935 or 13 per cent more than six years previously. Cancer of the uterus alone caused 15,853 or 82.5 per cent of these deaths.[1] There is little doubt that in many instances death might have been avoided, had these women realized the seriousness of their early symptoms and placed themselves under competent medical care before the disease had progressed to a hopeless stage.

We do not know the primary cause of cancer. We do know, however, that carcinoma will result from chronic irritation, for it has been produced experimentally in this way. Cancer developing in locations subjected to repeated injury or at the site of chronic inflammatory lesions is a quite common clinical observation. The physician's efforts in the control of cancer, therefore, must be directed, first, toward the eradication of known predisposing lesions, second, toward the detection of early cancer, third, toward prompt and efficient management as soon as a diagnosis is made, and fourth, toward cancer education of the public.

Gynecologic cancer may be avoided largely if chronic inflammatory processes and irritation be eliminated. Examples of such influences are cancer of the vulva which develops most frequently in women who have had chronic inflammatory diseases, such as leucoplakic vulvitis.[2]

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Ninety-five per cent of cancer of the cervix occurs in women who have damaged and diseased cervices.

Graves found only two women in 6,000 who had had cervical repairs and who later developed cancer of this structure. On the other hand, in cervical cancer he found less than 2 per cent who had had cervical injuries properly repaired.[3] In studying the histories of 375 women with cervical cancer, Lynch found only 6 who had had injuries of the cervix corrected.[4] Bland reports 13,747 patients, having damaged and diseased cervices, efficiently treated, with only 11 developing carcinoma.[5]

The value of periodic examinations in the control of cancer is being more widely appreciated as time goes on and statistics are accumulated. An outstanding study of this type in relation to uterine carcinoma is now being conducted by Dr. Catherine MacFarlane at the Women's Medical College of Philadelphia.[6] One thousand white women between the ages of 30 and 80 years are having such examinations at six-month intervals for a period of five years. Significant pathology has been found in 25 per cent of these volunteers, consisting of erosions or inflammatory lesions of the cervix, polypoid growths and leucoplakia. Four instances of early cancer have been found. Commenting on this work, Dr. Ludwig Hektoen, Director of the National Advisory Cancer Council in a personal communication, asks this question, "Would not projects of this kind for the most unfavorably situated of our women, tend to meet a great need?"[7]

The physician in his daily contact with women may do much to educate them regarding the value of periodic physical examinations.

Intelligent obstetric care is important in cancer control. The immediate repair of cervical injuries would close these gaping wounds of the cervix, which if left, become chronically infected and offer such a menace to the woman's future security. Such procedures may be done safely in hospitals, however, the risk of infection in homes seems too great to warrant repair under such conditions. This speaks for the wider use of hospitals in maternity care. Post-partum supervision offers an opportunity to correct significant pathology, such as extensive cervical lacerations, erosions, or endocervicitis. Through periodic examinations, the cervix should then be maintained in the healthiest condition possible.

The early diagnosis of gynecologic cancer is the physicians' great responsibility. Symptoms which give the slightest suspicion of malignancy demand an immediate investigation. The family physician here plays a most important role, for he is usually first consulted.

Because cancer of the uterus is the most common malignancy and its early diagnosis difficult to make, methods of early detection are important. Cervical carcinoma occurs five to six times as frequently as it does in the uterine body. Injuries and infection are undoubtedly responsible for its more frequent occurrence here.

The earliest gross appearance of cervical carcinoma is as a friable nodule, with the surface epithelium usually broken down or partially so, and any manipulation causes it to bleed. Such a malignant nodule eventually goes on to an everting or inverting type of growth, later to result in ulceration and crater formation. Unfortunately, most patients

are seen for the first time in an advanced stage of the disease. Seventy per cent of the 154 patients with cervical cancer seen in our clinic since 1930 showed the carcinoma to have spread definitely beyond the confines of the cervix.

Various attempts are being made to diagnose cervical carcinoma before such gross changes have occurred.

It is thought by Hinselmann, Schiller and others that beginning carcinomas have the appearance of leucoplakia before they can be recognized grossly. Hinselmann devised a colposcope which magnifies the mucosa of the cervix to aid in detecting such lesions. He reported having observed six patients with leucoplakia in 1926 who four years later developed cancer of the cervix.[8]

Schiller advocates the application of Grams iodine stain for the detection of such lesions. Normal cells stain a deep mahogany brown, while those of cancerous nature, due to their lack of glycogen, do not stain so well. Schiller believes that 30 per cent of all cases of beginning carcinoma give this whitish or unstained appearance. He further states that the earliest stage of cervical cancer is characterized by surface epithelium that has the cytologic characteristics of carcinoma. In 1937 he reported that he had discovered 130 cases of early carcinoma by this method. From 1928 to 1931 there were 51, of which 49 were alive and healthy, a five-year survival of 96 per cent.[9]

Because of considerable variation in thought of gynecologists and pathologists as to the practicability and value of these tests, the author secured a cross section of opinion of 11 teachers located in different centers of the United States and pre-eminent in the field of gynecologic cancer.

They were first questioned regarding their experience with the Schiller test, the percentage that had proved malignant, and what value they placed on this test as a means of early diagnosis. Many interesting and valuable comments were received.[10]

All had had experience with the test. As to the number of malignancies found, nine had either found none, very few, or were unable to say. Two made definite statements: The first, Lynch, having had 184 consecutive cases, found four early cancers without gross evidence of the disease. Three of these gave a positive Schiller test and the other did not. The second, Falls, using the routine test, states that when the test is positive, if an infected laceration is present, he removes a cone of cervix which is systematically studied. Not more than 5 per cent of these tissues showing a positive reaction proved to be cancerous.

Six men stated that the test was of value in identifying areas for biopsy, however, one of these, Miller, had given it up, after using it for some time, stating that it was of little additional help in his diagnostic work. The other 5 stated that they placed no value on it. Interesting comments were made on the biopsy findings, two stating that relatively few had proved malignant, another that the biopsies did not confirm the supposed cancer, and a fourth, that not all cervices giving positive tests have been proved cancerous and that not all cancerous cervices have given positive tests. Healy answered, "We have not picked up a single instance of cervical cancer with the Schiller Test."

It is obvious from the experience of these men who have all put the Schiller test to trial, that they have not been able to duplicate Schiller's findings of so many early superficial carcinomas. This makes one wonder if actual cancer was present in the 51 patients in whom Schiller reported a 96 per cent, five-year survival.

The chief value of this test seems to be in indicating suspicious areas from which biopsies may be taken and to demonstrate the involved mucous membrane at the edges of early carcinoma. A few early cancers have been found by this method which would not have been recognized grossly, therefore, the test merits recognition.

Questions were asked regarding the use and value of the colposcope. Only two of the eleven consider this instrument of enough value to use routinely. The objection voiced by one (Miller), who formerly used it a great deal and gave it up, is that it is open to the same objections found in high powered stethoscopes and like instruments. It has been our experience that the colposcope is time consuming and the findings difficult of interpretation. Strong illumination has most of its advantages and none of its disadvantages.

Finally, they were questioned as to their method of dealing with leucoplakia of the cervix. There was little variation of opinion here, nearly all advised biopsy, and if the lesion proved to be benign, destruction of the area with cautery, or surgical removal. From this, it is apparent that leucoplakia is universally looked upon with suspicion because of the uncertainty of its behavior; however, most stated they had seen but few such lesions.

At present, careful study of the cervix with the naked eye, under strong illumination, with biopsy of suspicious areas and microscopic examination, is the most dependable method of early diagnosis.

The early detection of carcinoma of the uterine body must necessarily be made by diagnostic curettage. Women in whom bloody vaginal discharge occurs after the menopause have carcinoma in most instances and the diagnosis should be considered cancer until curettage proves the presence or absence of malignant tissue. It is important to remember that cancer of the fundus may develop during menstrual life, manifesting itself by intermenstrual bleeding, and a diagnosis can only be made from an endometrial biopsy obtained by curettage. Twenty-five per cent of the patients in our clinic with recorded cancer of the fundus were still in menstrual life.

A better understanding on the part of physicians as to the proper methods of treatment would do much in the control of malignancies. This applies particularly to the limitations of surgery in cancer of the cervix. There is also need for improvement in the training of medical students in the management of this disease. Attendance at cancer clinics should be required and instructions given in methods of diagnosis and treatment. Cancer clinics in which the radiologist and roentgenologist, the pathologist, and the gynecologic surgeon cooperate in studying cases and directing the treatment are the most satisfactory. Following the initial treatment, such patients should be examined periodically for recurrent lesions, and the indicated treatment immediately instituted.

Realizing that the control of cancer in women at the present time is inadequate and unsatisfactory, the gynecologists of this country eagerly seek the cooperation of all lay or professional groups in reducing this high mortality rate. To those who have given serious thought to this subject, there is but one conclusion. This is the great need of education regarding cancer; education of women regarding the early signs and symptoms, education of physicians in the methods of early diagnosis and proper manner of treatment, and education of hospital administrators as to the need of proper equipment to aid the physician in carrying out these measures. The American Society for the Control of Cancer has ably waged a campaign of education for more than twenty-five years. Despite their efforts toward making women symptom conscious, there are still large numbers who disregard the danger signals.

Because vaginal discharge and bleeding are the earliest manifestations of most gynecologic cancers, a campaign of education of what to expect and what not to expect during menstrual life should be waged relentlessly until it reaches all classes of individuals. The majority of women in our clinic with uterine cancer are seen for the first time in an advanced stage of the disease. In discussing this fact with such patients, there seems to be several reasons for this delay. (1) Women are accustomed to vaginal discharges, so place little importance to this occurrence unless it produces discomfort, or hemorrhage occurs. (2) It is customary for them to ascribe such symptoms to the change of life, if they be anywhere near that age. (3) They seek advice from older women who comfort them by saying they had experienced similar symptoms at this time of life. (4) They unfortunately experience no pain in the early stages, important because discomfort would cause them to seek medical advice which might save them from a cancer death. (5) Some fear the diagnosis and the possibility that an operation might be advised. (6) The cost of the physician's examination prevents others from having an investigation, for to them, they have what seems but trivial symptoms.

If we accept these observations as true and hope to correct such erroneous ideas, it is my opinion that we must give our whole-hearted support to educational movements. A comprehensive course in female physiology as it pertains to the genital organs could well be a required high school subject for all girl students. Such a course should not only include the normal physiology but emphasize the possible significance of the abnormal in its relation to malignant disease. The importance of the physicians' early investigation of abnormal discharges or bleeding from the genital organs, especially those occurring during the third, fourth, and fifth decades of life, should be particularly stressed. There is little excuse for not educating young women regarding the behavior of this fatal disease. Our inability to conquer the cancer problem, lies in the fact that women in general do not appreciate the significance of the early symptoms of carcinoma. Were such a course established, such teaching should result in a better informed, more cooperative class of women later in life. They would understand the necessity of periodic examinations and of consulting a competent physician at the first ap-

pearance of significant symptoms. The physician has but little chance to help unless the patient presents herself early in this disease. A recent statement by a New York journalist clearly sums up the situation as it exists today, "We are faced with the paradox that the most important part of the cancer fight, lies in the nonmedical field, that all of the radium, x-rays and most skillful surgery in the world are of no avail unless the public can be educated."

CONCLUSIONS

1. Physicians should instruct their women patients to undergo periodic examinations, at which time a careful investigation of the pelvis should not be omitted. Strict attention should be paid to the elimination of chronic inflammatory lesions.

2. The immediate repair of cervical injuries following childbirth should be done when surroundings permit. The post-partum elimination of cervical erosions, endocervicitis, and infected lacerations are important in the prevention of cancer.

3. In the experience of a number of leading American gynecologists, the value of the Schiller test is uncertain and doubtful.

4. The colposcope is but little used, owing to the difficulty of the interpertation of its findings.

5. At present there is no substitute for strong illumination as an aid in detecting early evidence of cervical malignancy. Biopsy and microscopic examination of any suspicious appearing lesion should be promptly performed.

6. There is general agreement that when leucoplakia of the cervix is found, it should be eradicated.

7. A more thorough and systematic training of medical students in the early diagnosis and treatment of cancer is advisable.

8. There is need for wider education of women as to the significance of abnormal menstruation and vaginal discharges. Such education of girls of high school age is suggested.

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833 Eleventh Street, S. W.

Note: For lack of space it is not feasible to publish all of the papers presented at this Congress. Many of these were introductory to Round Table Discussions. A selected number is included in this issue of the Journal and another group may be found in the January, 1940 number of the *Western Journal of Surgery, Obstetrics and Gynecology.* A general summary of the proceedings of the Congress is presented in Dr. F. L. Adair's article published in the October, 1939 issue of the Journal, and a special summary of the obstetric papers may be found in the article by Dr. G. C. Schauffler in the present issue. Complete Proceedings of the Congress may be published at a later date by the American Committee on Maternal Welfare.

THE DETECTION OF THE RUPTURE OF FETAL MEMBRANES WITH THE NITRAZINE INDICATOR*

TOM ABE, M.D., M.Sc. (MED.), LOS ANGELES, CALIF.

THE obstetrician is frequently confronted with the question of whether or not the bag of waters has ruptured, and much hinges on this point as to the subsequent course of treatment. In particular, this knowledge carries great weight as to the advisability of performing a cesarean section. The patient's word that she has been dripping water cannot be used as a criterion, as frequently in the later stages of pregnancy a relative incontinence develops as the fetal head settles down against the bladder. A large amount of cervical and vaginal mucus may be interpreted as leakage of amniotic fluid. Thus a test by which this information can be accurately determined would be of great value.

In recent years several such tests have been reported, all with an uniformly high percentage of accuracy. The most popular scheme relied upon the alteration in the hydrogen ion concentration of the vaginal vault, occurring subsequent to the passage of amniotic fluid from the amniotic sac. Temesvary[1] (1933) was among the first to perceive the value of this change and applied it to a clinical purpose. He used an indicator dye, bromthymol blue, to detect the change in pH, and out of 131 cases he reported an error of only 5 per cent. Berlind[2] (1932), Bock[3] (1934), and King[4] (1935) supported this high percentage of accuracy with their statistical evidences. Philipp[5] (1929) sought for lanugo and uric acid crystals under the microscope to determine whether or not the bag of waters had broken. Numers[6] (1936) based the identification of fat particles of the vernix caseosa in the vagina as a sign of the rupture of the sac.

In the Los Angeles County General Hospital Obstetrical Service the bromthymol blue test as described by King was used on a number of questionable cases of ruptured membranes. King used sterilized cotton applicators that have previously been dipped in 0.2 per cent bromthymol blue (dibromthymolsulphonphthalein) in alcoholic solution. The applicator was inserted into the vagina for one minute and the change in color from orange to blue green denoted rupture of the fetal membranes. Color unchanged signified intact membranes. He reported one false positive out of 141 patients with intact membranes, and nine false negatives from 161 patients with membranes ruptured; a percentage accuracy of 99.3 per cent and 94.7 per cent, respectively. Although no statistical studies were made of King's test at this institution, the accuracy of the test in many cases was not comparable to that of King's report. The frequent occurrence of false negatives rendered the value of the test questionable.

*Studies made and data collected at the Los Angeles City Maternity Service and the Obstetrical Department of the Los Angeles County General Hospital, 1937 to 1938.

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The purpose of this paper is to show the results of a similar test that is identical in principle, but employing a different indicator dye and some modification in technique. The indicator used was nitrazine (sodium dinitrophenylazonaphthol disulphonate) test solution which is now available on the market.

PRINCIPLE OF THE TEST

The normal reaction of the vaginal secretions is acid. Temesvary demonstrated by colorimetric methods the pH range of the vagina in pregnant women at term to vary from 6.0 to 5.2. Using hydrogen ion electrode, Bock corroborated with similar figures. Whereas, in women with ruptured membranes the former found the pH to be 6.0 to 8.1, and the latter reported the rise in pH to be 6.8 to 8.2.

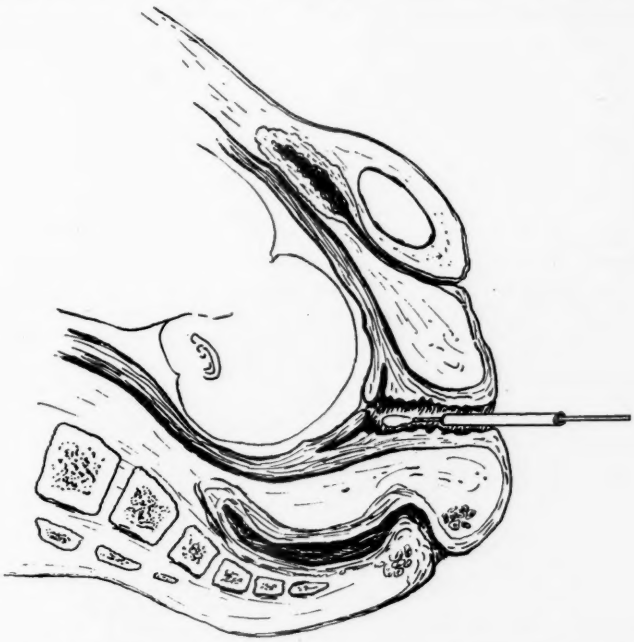

Fig. 1.—Showing position of glass tubing through which the dyed cotton applicator is inserted.

Thus the nitrazine indicator which offers the sharpest end point between 6.4 and 6.8 should be an ideal indicator for detecting any alteration in vaginal pH due to the entrance of amniotic fluid from a ruptured sac. The abrupt end point at such a narrow range is theoretically a better indicator dye to employ than bromthymol blue which changes from orange to blue green at a pH of 6.0 to 7.7.

TECHNIQUE

Ordinary cotton applicators are dipped in nitrazine test solution and then dried. Upon evaporation the dye yields a canary yellow color with scattered streaks of green. This is the neutral point at about pH 6.6. A dyed cotton applicator and a short glass tubing, the purpose of which will be explained later, are placed in a large size test tube and stoppered with a cotton plug. This is then autoclaved. The test tube container is used purely for convenience, as it can be kept in the labor room for immediate availability or carried around as part of the doctor's equipment.

In performing the test after proper antisepsis of the vulva, the labia are widely separated and the sterile glass tubing (0.5 inch diameter and 3.5 inches long) is inserted into about one-third distance of vaginal tract. Through this tubing the dyed applicator is passed until it approaches the site near the external os where amniotic fluid should be of the greatest concentration if rupture of the membranes has occurred. Thus the glass tubing has a twofold purpose: To allow a sterile introduction of the dyed applicator high into the vaginal vault, and to obtain a correct pH reading of the vagina not affected by urine which may have trickled down over the introitus. The applicator is left in the vagina for thirty seconds, removed, and change in color is noted. Interpretations of the color changes are as follows:

Yellow	pH 5.0	Intact membranes
Olive yellow	pH 5.5	
Olive green	pH 6.0	
Blue green	pH 6.5	Ruptured membranes
Blue gray	pH 7.0	
Deep blue	pH 7.5	

As a rule the change in color on the applicator is complete, a change only on a portion of the cotton tip speaks for intact membranes. This is not so with the bromthymol blue indicator in which a tiny speck of green, which can easily be overlooked, occurs with the break in the bag of waters. This is one of the advantages of nitrazine dye over bromthymol blue. Any change in color of the applicator to that containing a bluish hue, whether it be blue green, blue gray, or blue black indicates a pH of 6.8 or higher which in all probability is due to a spill of the amniotic fluid into the vaginal tract. Color changes of olive green to all shades of yellow indicate a pH on the acid side due to the non-entrance of the amniotic fluid and which is the normal reaction of the vagina.

RESULTS

The test was performed on a large number of out-patients on the Los Angeles County Maternity Service and in-patients on the Obstetrical Service of the Los Angeles County General Hospital. These patients were all at term or in labor with or without suggestive history of ruptured membranes. For comparative study and evaluation, both the nitrazine and bromthymol blue indicators were used simultaneously on all patients examined. The ultimate check-up on the actual condition of the membranes was determined by vaginal examination for the presence or absence of the bag of waters when the patient was placed on the table for delivery, or by noting when definite rupture occurred as manifested by a sudden break in the membranes and visualization and smell of the amniotic fluid. Thus the relative accuracy of the tests was determined in each case, and the results were interpreted as being true or false.

When the indicator showed a change in pH toward the alkaline side due to ruptured membranes, giving a positive result which was later verified, it was considered as a true positive. But if a positive result appeared in a patient with known intact membranes, it was classed as a false positive. Conversely, if the indicator dye did not produce any change toward the alkaline side in a case subsequently proved to have intact membranes, it was interpreted as a true negative. And if the test failed to demonstrate a change to the alkaline side in a case with definitely ruptured membranes, it was classed as falsely negative.

A total of 176 patients, approaching or in labor, were given these tests. For the nitrazine test, 97 indicated rupture of the membranes and were recorded as positive, and 79 showed intact membranes and were marked as negative. Of the 97 positive results 96 (98.9 per cent) proved to be true, and in only one case the test revealed a falsely positive outcome. Seventy-six (96.2 per cent) of the 79 negative cases turned out to be correct with three giving false results. The combined accuracy of the true positive and the true negative results was 97.7 per cent.

TABLE I. NITRAZINE TEST

NUMBER OF CASES	REACTION	TRUE	FALSE	PER CENT ACCURATE
97	Positive	96	1	98.9
79	Negative	76	3	96.2
Total 176		172	4	97.7

For the bromthymol blue test 86 of the 176 cases showed the bag of waters to be broken. Eighty-four (97.6 per cent) of these were revealed to be true later and two were false. Ninety of the cases tested with this dye indicated intact membranes, but only 76 (86.6 per cent) were verified to be true and 14 proved to be false, the combined accuracy of the true positives and the true negatives of this group being 90.9 per cent.

TABLE II. BROMTHYMOL BLUE TEST

NUMBER OF CASES	REACTION	TRUE	FALSE	PER CENT ACCURATE
86	Positive	84	2	97.6
90	Negative	76	14	86.6
Total 176		160	16	90.9

DISCUSSION AND CONCLUSION

It is to be noted that both the nitrazine and bromthymol blue tests gave an uniformly high percentage of accuracy (98.9 per cent and 97.6 per cent, respectively) in indicating rupture of the bag of waters as manifested by their change in color of the dye. The results with the bromthymol blue tests in this research conform closely to the findings reported by King in respect to true positives (he reported 94.7 per cent). It can be certain then that a positive result in either of these tests speaks very strongly for ruptured membranes and clinically can be assumed as such.

However in those patients with intact membranes, the occurrence of false negatives was more frequent in the bromthymol blue test (14) as compared with the nitrazine test (2). And in both of the cases where false negatives occurred in the nitrazine test group, the results were likewise false with the bromthymol blue test. Thus, in general, the bromthymol blue test did not measure up to the accuracy of the nitrazine test in a good many cases. The relatively frequent occurrence of the falsely negative results with bromthymol blue test in patients having ruptured membranes perhaps may be explained. King attributes this discrepancy to insufficient amount of amniotic fluid, due to its draining off or to settling of the infant's head to prevent further flow, or to the fact that "natural vaginal acidity had reasserted itself." Due to the fact that the nitrazine test proved to be accurate in 98.9 per cent of the cases where the membranes were ruptured, this dye speaks for greater sensitivity of the nitrazine dye because of its sharper and slightly lower end point. It may be that the amount of the amniotic fluid spilled into the vaginal vault was insufficient to cause any change in the bromthymol blue dye, but sufficient to alter the hue of the nitrazine from yellow to a blue green color.

The technique of using the short glass tubing as a protective cylinder through which the sterile applicator stick with its cotton and dye in-

dicator was passed proved to be a valuable modification. Care must be used in its insertion, as otherwise it may be painful and injurious. It must be certain that its ends have been flamed over the Bunsen burner to smooth off its edges. It is of importance that some form of antiseptic preparation of the external genitalia be made previous to the introduction of the glass tubing. Type of antiseptic used will have no effect on this test, as the dyed cotton applicator is inserted beyond reach of any antiseptic solution. In using this sterile tubing as an aid in inserting the dyed applicator into the vaginal vault, there was not a single case of post-partum infection in those patients tested.

SUMMARY

1. A modification of a test to determine rupture of fetal membranes, using the principle of alteration of the vaginal pH following the rupture of membranes, is presented. The test involves the use of a new indicator dye, nitrazine (sodium dinitrophenylazonaphthol disulphonate), and a technique which is sterile and avoids the influence of urine and antiseptic solutions on the indicator dye.

2. One hundred seventy-six patients from the Los Angeles City Maternity and Obstetrical Services of the Los Angeles County General Hospital were given this test and the bromthymol blue test simultaneously, and comparative studies were made regarding their accuracy.

3. The nitrazine test was found to give greater accuracy in those patients where the membranes were not ruptured, as its percentage accuracy for true negatives was 96.2 per cent in comparison with the bromthymol blue test which was 86.6 per cent. In those patients tested with known ruptured membranes, both tests gave equally accurate results, 98.9 per cent and 97.6 per cent, respectively.

4. No post-partum infection followed any patient tested with this technique.

REFERENCES

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Stimulated by an article by B. Otton (Zentralbl. f. Gynäk. 1929) in which a supposedly unknown photograph of Semmelweis was published, the author has assembled and reproduced all pictures available at present. These are documented and will be of value to the historian. Among the pictures is an oil painting of dubious authenticity, representing Semmelweis as a lad of 12 to 14 years. A copy of a photograph not previously published, and taken in 1858, is reproduced. Two little known photographs, taken in 1863 and 1864, are of interest in their demonstration of the effects of Semmelweis' struggle for recognition of his work and of the ravages of the disease from which he must have been suffering at that time. Altogether nine pictures are nicely reproduced and traced.

J. L. McKelvey.

ESTROGEN AND PROGESTIN METABOLISM IN PREGNANT WOMEN*

With Especial Reference to Pre-Eclamptic Toxemia and the Effect of Hormone Administration

George Van S. Smith, M.D., and O. Watkins Smith, Ph.D.,
Brookline, Mass.

(From the Fearing Research Laboratory, Free Hospital for Women)

AN ENDOCRINE imbalance in pre-eclamptic toxemia, eclampsia, and certain cases of premature delivery has been definitely indicated by our previous quantitative studies.[1-5] Our earlier investigations revealed excessive chorionic gonadotropin and low levels of estrogen in the serum and urine of patients exhibiting these disorders. Later the abnormal rise in serum chorionic gonadotropin was found to precede clinical signs by some weeks. With improved methods for extracting and separating urinary estrogens, it became possible to gain more information concerning their metabolism in women. Progestin appeared to be necessary for their normal metabolism and utilization, and in the absence of sufficient progestin they appeared to be more rapidly destroyed.[4, 6, 7] It seemed possible, therefore, that the explanation for low levels of estrogen in pre-eclamptic patients might lie in a progestin-deficiency with a resultant increased destruction of estrogens. Preliminary studies of urinary pregnanediol, estrone, estriol, and "x" estrogen† in pre-eclampsia gave evidence that a progestin, as well as an estrogen, deficiency did follow the abnormal rise in chorionic gonadotropin and that the onset of clinical signs was accompanied by the marked shift in the distribution of urinary estrogens, which we have come to associate with a more rapid destruction due to progestin-deficient metabolism.[4]

The demonstration of a typical hormonal imbalance involving an estrogen and progestin deficiency has seemed to warrant the administration of these two substances in the hope of re-establishing a normal balance. If this were accomplished and accompanied by clinical benefit, one would have some basis for assuming that the disturbances were the direct result of some change associated with a progestin-deficient metabolism of the estrogens. Furthermore, the quantitative determination of chorionic gonadotropin and estrogen in the serum and of estrone, estriol, estradiol, and pregnanediol in the urine, before and after the administration of large amounts of estrogen and progesterone, could

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†The discovery of this third estrogenic factor in urine and data concerning its physiologic significance are reported in reference 4. On Dec. 1, 1938, we submitted to Dr. E. A. Doisy the estrone fraction from 38 liters of urine from women during labor and delivery. On Aug. 21, 1939, Dr. Doisy informed us that he had isolated and identified dihydrotheelin (estradiol) in this material.[10] It seems safe to assume, therefore, that most of the nonketonic potency of estrone fractions (our so-called "x" estrogen) is accountable to estradiol.

not fail to yield considerable valuable information concerning the metabolism of these hormones. From these ideas the present investigation evolved.

METHODS

For the determination of chorionic gonadotropin and estrogen in the serum, 40 c.c. of venous blood are taken without any anticoagulant, the clot allowed to form, and the serum separated. Chorionic gonadotropin is extracted and assayed by the method recently described.[5] More animals are used than were recommended in this publication, in order to obtain a closer end point. The serum remaining after chorionic gonadotropin assay (usually 15 to 20 c.c.) is accurately measured and precipitated with about 5 volumes of ethyl alcohol for the extraction of estrogen. After standing twenty-four hours or longer, the alcohol is removed by centrifugation, the precipitate thoroughly washed twice with alcohol and twice with ether, and all solvents are combined and evaporated to dryness. The residue is taken up in normal saline solution (using a rubber policeman and frequent washings with saline) and made up to a measured volume with saline. After shaking to a smooth emulsion, aliquot portions are assayed on mature spayed female rats, following the previously described technique.[7] It has been found necessary to extract the serum, since the large amounts necessary to give a positive test have occasionally proved toxic. The test is not thoroughly satisfactory because the limited amount of serum does not permit as many assays as are desirable for reaching an end point. Attempts to obtain higher values for serum estrogen, such as through hydrolyzing the serum itself (by acid hydrolysis or by incubation) or through butyl alcohol extraction followed by acid hydrolysis of the evaporated extract, have been unsuccessful. The method described yields values which agree with assays on the straight serum and appears to give information of physiologic significance.

For the determination of pregnanediol and the estrogens, a twenty-four-hour specimen of urine is collected and extracted within twenty-four hours of the time of collection. It is our habit to perform a creatinine determination[8] on each specimen and keep a record of the twenty-four-hour creatinine output for each patient followed. Since the daily excretion of creatinine for any individual is relatively constant, any gross error in a twenty-four-hour collection can be readily detected and a value closely approximating the true twenty-four-hour volume calculated.

Sodium pregnanediol glucuronidate has been gravimetrically measured according to the method of Venning.[9]

An exact description of the method now employed by us for determining estrone, estriol, and "x" estrogen, i.e., estradiol, in human urine is being separately published.[10] Although the method of separation is not strictly quantitative, recovery experiments[10] have indicated that most of the potency designated as estrone, estriol, and estradiol is accountable to these three hormones, respectively. The technique of bio-assay has been described in a previous publication.[7] Inasmuch as our animals are standardized against crystalline estrone, estriol, and estradiol, the results below are expressed in terms of weight as well as rat units. The amount of estradiol benzoate administered is converted in the charts into milligrams of estradiol, the latter being 72 per cent of the former.

Because of the high incidence of pre-eclamptic toxemia and premature delivery in diabetic women, we have concentrated on these patients in following hormonal changes prior to clinical manifestations. Comparative assays of serum and urine from diabetic and nondiabetic pregnancies have revealed no essential difference in the chorionic gonadotropin or estrogen changes of these two groups, either throughout normal pregnancy or before and during the development of late pregnancy toxemia or premature delivery.[3, 5] The fact that most of the patients herein studied were diabetics, therefore, does not influence either the

findings or the applicability of the conclusions to similar conditions in nondiabetic pregnant patients.

EXPERIMENTAL

In Table I a fairly complete study from the third month of a normal pregnancy to delivery is recorded. The values for chorionic gonadotropin and estrogen of the serum agree with those already published. The rise in serum chorionic gonadotropin during the last four weeks has been observed in other normal pregnancies. The urinary pregnanediol falls well within the limits of the values published by Venning[11] (a composite curve of 210 specimens from 8 women at various stages of pregnancy). It is interesting to observe that from the twenty-fifth week on, when specimens were analyzed every two weeks, waves in the pregnanediol curve become apparent with peaks at four-week intervals and delivery when it is on the downward trend. The urinary estrone curve shows waves and troughs coincident with those of pregnanediol. Hormonal rhythms in pregnancy have been mentioned before, but their cause can at present be only surmised. Estradiol does not vary significantly until labor, when its rapid rise is accompanied by a relatively sudden decrease in estriol, which up to this time had been steadily increasing, and *the complete disappearance of estrone*—changes which we associate with a reduction of progestin.

TABLE I. NORMAL PREGNANCY

E. B. F., aged 33 years, grav. i, last catamenia April 18, 1938, due Jan. 23, 1939

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C.		URINE—24-HOUR EXCRETION						
		C. G.†	ESTRIN	PREGNANEDIOL MG.	ESTRONE R.U.	ESTRONE MG.	ESTRADIOL R.U.	ESTRADIOL MG.	ESTRIOL R.U.	ESTRIOL MG.
7/12-14/38	12	100	<20	9.0	50	0.033	450	0.0225	1,000	0.5
8/ 7- 8/38	16			11.7	250	0.166	1,000	0.05	4,000	2.0
9/10-11/38	21			36.0	670	0.445	1,330	0.066	8,000	4.0
10/12-13/38	25½	100	20	58.3	700	0.465	2,000	0.10	15,000	7.5
10/23-24/38	27			44.9	400	0.267	1,330	0.066	20,000	10.0
11/ 6- 7/38	29	100	33	73.2	1,330	0.89	1,330	0.066	20,000	10.0
11/20-21/38	31			65.6	400	0.267	1,200	0.06	20,000	10.0
12/ 4- 5/38	33	100	50	82.9	1,000	0.667	1,500	0.075	22,500	11.1
12/18-19/38	35	200	50	78.5	330	0.22	1,000	0.05	25,000	12.5
1/ 2- 3/39	37	200	75	99.4	1,000	0.667	1,000	0.05	53,000	26.5
1/15-16/39	39	200	75	91.7	670	0.45	1,330	0.066	60,000	30.0
1/18/39*	39½	333	50		0		4,000	0.2	20,000	10.0
Spontaneous labor followed by normal delivery.										

*Specimen collected during labor, twenty-four-hour volume calculated on basis of creatinine, not enough for pregnanediol determination.

†C. G., Chorionic gonadotropin.

The fact that a rise in serum chorionic gonadotropin has been detected during the last weeks of pregnancy, together with the observation that a deficiency of both estrogen and progestin pertains at the time of spontaneous delivery, introduces an apparent paradox, since the pregnancy gonadotropic factor characteristically stimulates the production of these 2 steroids in experimental animals. A possible interpretation, based on considerations which have been previously discussed,[5] is that chorionic gonadotropin is actively utilized in the elaboration of estrogen and progestin and that a failure in such utilization is reflected by increasing amounts of this hormone in the circulation.* On this basis, if

*We have recently had called to our attention the fact that an active utilization of chorionic gonadotropin in the placenta for the production of estrogen and progestin was suggested by Browne and Venning in 1936.[20]

a progestin-deficient metabolism of the estrogens is concerned in the initiation of labor, the primarily responsible change would be a failing utilization of chorionic gonadotropin for the elaboration of these steroids.

Analyses of single twenty-four-hour specimens of urine from 3 pre-eclamptic women and 3 normally pregnant at approximately the same period of gestation (thirty to thirty-eight weeks) were performed. The urines from pre-eclamptic patients were featured by low pregnanediol (an average of 31 mg. as compared with an average of 108 mg. in the normals), complete absence of estrone (as compared with an average of 1.5 mg. in the normals), high estradiol (an average of 0.2 mg. as compared with an average of 0.13 mg. in the normals), and low estriol (an average of 14 mg. as compared with an average of 39 mg. in the normals), these changes being entirely similar to those observed at the time of normal labor. Thus the same progestin-deficient metabolism of the estrogens which appears to accompany labor seems, when it occurs prematurely, to be closely associated with pre-eclampsia.

The sequence of the endocrine changes which preceded and accompanied pre-eclampsia in an untreated patient have already been published.[4, Chart 5] In this case the abnormal rise in serum chorionic gonadotropin was first noted at twenty-two weeks. At twenty-eight weeks high chorionic gonadotropin was still the only demonstrable abnormality. Two and one-half weeks later, however, when urinary albumin was first noted, a marked rise in urinary estrone failed to be accompanied by a corresponding increase in estriol excretion, indicating failure in conversion of estrone to estriol, due to progestin-deficiency. Such a deficiency was borne out by a drop in urinary pregnanediol. A sudden increase in the severity of clinical signs three days later was accompanied by an equally sudden shift in the hormonal findings, namely, a drop in serum estrogen, urinary pregnanediol, and estriol, a rise in estradiol and *the complete disappearance of estrone.* It is impossible to interpret these shifts of excreted estrogen as reflecting failure of conjugation or kidney retention. The rise in urinary estradiol and the diminished serum estrogen argue against this explanation. The most satisfactory interpretation is that a failure in the conversion of estrone to estriol resulted from a decreasing elaboration of progestin and that the withdrawal of sufficient progestin-protection finally resulted in rapid destruction of estrogens, as indicated by the sudden complete disappearance of estrone.

Mrs. M. W. (Table II) had been studied by us through a previous pregnancy,* in which pre-eclampsia had been terminated by intrauterine fetal death. The pregnancy covered in this table was very briefly summarized in 1938.† Pre-eclampsia was predicted by the rising chorionic gonadotropin and preceded by a lowered excretion of pregnanediol and all 3 estrogens. The findings are in keeping with the assumption that a failure in the utilization of chorionic gonadotropin was resulting in decreasing, rather than the normally increasing, elaboration of estrogen as well as progestin with advancing pregnancy. An unprecedented situation accompanied the onset of toxemia, the disappearance of all the urinary estrogens. This applied to 4 specimens collected during the week of December 23 to 29. On December 22 the patient had been in mild diabetic coma. We wonder if some urinary constituent associated with this incident may have either destroyed estrogens or rendered the method of hydrolysis or extraction ineffective. Of all the urines from pregnant women that we have tested for estrogens by any method, these are the only ones in which no estrogenic potency has been found. The presence of serum estrogen demonstrates that estrogen was still present in the circulation. The lowered values in the serum at this time indicate that estrogens were not being retained by the kidney. After ten days of treatment (totaling 55 mg. of estradiol benzoate and 200 mg. of progesterone) instigated by the appearance of mild clinical signs and the preceding rise in chorionic gonadotropin, estrogens re-appeared in the urine. In

*Smith and Smith: Ref. 3, charts 5 to 8, Mrs. Wh.

†Smith and Smith: Ref. 4, paragraph 3, p. 780.

TABLE II. DIABETES, PRE-ECLAMPSIA, HORMONAL TREATMENT

Mrs. M. W.,* aged 34 years, gravida ii (pre-eclampsia and stillbirth with first pregnancy), last catamenia May 16, 1937, due Feb. 20, 1938

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C.		URINE—24-HOUR EXCRETION							PARENTERAL INJECTIONS		CLINICAL NOTES		
		C.G.†	ESTRIN	PREGNANEDIOL MG.	ESTRONE R.U.	ESTRONE MG.	ESTRADIOL R.U.	ESTRADIOL MG.	ESTRIOL R.U.	ESTRIOL MG.	ESTRADIOL MG.	PROGESTERONE MG.	BLOOD PRESSURE	ALB.‡	EDEMA
9/27/37	19	50	<20										110/80	0	0
11/ 5/37	25	200	33	73	1,700	1.12	3,300	0.165	30,000	15.0			110/80	0	0
11/22/37	28	200	33	66	1,000	0.67	2,000	0.10	30,000	15.0			110/80	0	0
12/ 9/37	30½	333	33		600	0.40	1,400	0.07	20,000	10.0			110/80	0	0
	Admitted to hospital 12/20 because of edema and excessive gain in weight												In diabetic coma 12/22—nausea and uterine cramps		
12/23/37	32½	500	20	51	0		<100		<100				120-130/80-90	T	+
12/24/37											7.2	20	120-130/80-90	ST	0
12/25/37											3.6	20	110/70	SPT	0
12/26/37	33	333	20	60	0		<100		<100		3.6	20	110-120/70-90	SPT	0
12/27/37											0	20	120/80	SPT	0
12/28/37				64	0		<100		<100		7.2	20	140-110/90-80	ST	0
12/29/37		200	33	67	0		<100		<100		3.6 daily	20 daily	150-110/110-80	0	+
↓											↓	↓			
1/ 3/38				104	500	0.335	1,000	0.05	15,000	7.5	7.2	20	140/90	ST	0
1/ 4/38	34	100	66								7.2	20	120/80	T	0
1/ 5/38				91	500	0.335	500	0.025	35,000	17.5	3.6	10	120/80	ST	0
1/ 6/38											3.6	10	130-110/80	0	+
1/ 7/38				85	600	0.4	2,000	0.10	30,000	15.0	3.6	10	130-140/80-90	0	0
1/ 8/38				92	600	0.4	1,000	0.05	40,000	20.0	7.2	10	120/80	SPT	0
1/ 9/38		100	100								3.6	10	110-120/80-90	SPT	0
1/10/38	35												Delivered by cesarean section. Baby lived		

*Ref. 18, Case 27.

†C. G., chorionic gonadotropin.

‡T, trace; ST, slight trace; SPT, slightest possible trace.

TABLE III. DIABETES, PRE-ECLAMPSIA, HORMONAL TREATMENT

Mrs. MacD.,* aged 36 years, gravida iii (one normal pregnancy four years before onset of diabetes, one miscarriage since onset of diabetes), last catamenia unknown. Stillbirth about 4 weeks before term

DATE	WEEKS PREGNANT (APPROX.)	SERUM		URINE—24-HOUR EXCRETION						PARENTERAL INJECTIONS		CLINICAL NOTES				
		R.U./100 C.C.		PREGNANEDIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRADIOL	PROGESTERONE	BLOOD PRESSURE	ALBUMIN‡		EDEMA	MISCELLANEOUS
		C. G.†	ESTRIN		R.U.	MG.	R.U.	MG.	R.U.	MG.	MG.	MG.		QUAL.	GM. 24°		
4/10/38	12	100											110/80	0			
6/ 7/38	20	200											110/80	0			
7/15/38	25½	333+		15.2	33	0.02	133	0.007	5,000	2.5				ST		+	Nausea, abdominal pain, headache
7/21/38	26½	500	33	14.7	0		250	0.013	5,000	2.5			100/80	ST	1.5	+	Nausea, abdominal pain, headache
7/22/38											3.6 daily	10 daily					
7/29/38	27½				0		1,000	0.05	5,000	2.5	↓	↓	100/90	SPT	1.4	+	No subjective symptoms
8/ 4/38	28½	100	50	18.3	400	0.27	1,200	0.06	8,000	4.0	↓	0	100/60	SPT	0.4	±	Nausea, abdominal pain
8/ 9/38	29			17.7	500	0.33	1,500	0.075	8,000	4.0	↓	↓	90/60	SPT	0.7	±	Nausea, abdominal pain
8/11/38	29½	100	50	17.0	300	0.20	1,300	0.065	8,000	4.0	↓	10 daily	90/60	SPT	1.0		Nausea, abdominal pain
8/18/38	30½			24.6	800	0.54	800	0.04	13,000	6.5	↓	↓	110/70	T	5.6	+	No subjective symptoms

8/20/38		50	75								3.6 alt. days ↓	10 alt. days ↓				No subjective symptoms
8/25/38	31½			26.0	1,500	1.0	1,000	0.05	16,000	8.0	3.6 daily ↓	10 daily ↓		ST	0.9	0	No subjective symptoms
9/ 1/38	32½			0‡§	2,000	1.33	2,000	0.10	20,000	10.0	0	0	100/60	SPT	0.6	0	No subjective symptoms
9/ 8/38	33½	200	50	23.0	500	0.33	1,500	0.075	8,000	4.0	↓	↓	110/70	SPT	0.2	+	No subjective symptoms
9/13/38											3.6 daily ↓	10 daily ↓					No subjective symptoms
9/17/38	34½	100	75	36.4	1,300	0.87	1,300	0.065	16,000	8.0	0 ↓	0 ↓	100/60	0	0	0	No subjective symptoms
9/27/38	36																Stillbirth

*Ref. 18, Case 30.

†C. G., chorionic gonadotropin.

‡T, trace; ST, slight trace; SPT, slightest possible trace.

§Occasionally no sodium pregnanediol glucuronidate is found, presumably due to some unusual hydrolysis. This specimen had been kept cold during collection and extracted within twenty-four hours.

spite of the injected estrogen, the level was lower than it had been four weeks earlier, indicating destruction as well as diminished elaboration. During this time toxemia had, if anything, become more severe. By the following week the hormonal picture was entirely normal. A little albuminuria was the only clinical sign. Elective cesarean section was performed, and a healthy baby was delivered and survived. The patient's toxemia was never more than mild, so that no committal may be made concerning any salutary effect from injections. Considering her previous history and the abnormal endocrine situation at the onset of signs, the early initiation of therapy may have warded off a more serious situation, especially since there appears to be a correlation between the clinical changes and the endocrine values.

Mrs. MacD. (Table III), who had had one miscarriage since the onset of diabetes, was first seen when approximately three months pregnant. Due to catamenial irregularity, she could not be sure that a period had preceded conception. The serum chorionic gonadotropin at about the twentieth week showed an abnormal rise. Five and one-half weeks later the patient entered the hospital with mild but definite clinical signs. The findings at this time and one week later were typical of the pre-eclamptic pattern. The indications are that both progestin and estrogens were being elaborated in subnormal amounts for this period of gestation. The rise in estradiol between July 15 and 21, accompanied as it was by the disappearance of estrone and a failure of estriol to increase, indicates further that much of the secreted estrogen was not being properly metabolized and was being rapidly destroyed. Even after two weeks of the daily injection of 5 mg. of estradiol benzoate and 10 mg. of progesterone, there was very little increase in the urinary estrogens and pregnanediol. It would appear that this patient was destroying progestin as well as estrogen. By September 1, after six weeks of hormone administration, estrogen metabolism appeared to be normal and the patient was symptom free, the only toxic sign being a very small amount of urinary albumin. The recrudescence of serum chorionic gonadotropin and lowered excretion of estrogens and pregnanediol a week after all injections had been omitted (September 8) supply evidence in favor of the assumption that the changes observed during injections were the result of therapy. Four days of injections, beginning on September 13, were again followed by a change in the direction of normal. By September 17 the patient was clinically well. Ten days after the discontinuation of all therapy the common diabetic accident, stillbirth, occurred a few hours after intrauterine death. Unfortunately, the patient had left the hospital after the last injection, so that we have no information concerning the clinical and endocrinologic changes from that time through the accident.

The administration of hormones to this patient was apparently inadequate for the degree of estrogen and progestin deficiency that pertained. Yet, with prolonged treatment, there was some evidence for a more normal elaboration and metabolism of these steroids, accompanied by the disappearance of toxic signs. With toxemia as mild as hers, it might well be argued that clinical improvement would have occurred without hormone administration. Whether the injections postponed stillbirth and might have prevented it entirely had they been continued is entirely speculative.

Because of its close chemical relationship to the female sex steroids, especially progesterone, its similarity to progesterone in a number of physiologic effects,[12-16] and its availability in larger dosage, testosterone propionate was used as a substitute in the following 2 therapeutic trials.

Mrs. A. R. (Table IV) was a diabetic in whose previous pregnancy preeclampsia and stillbirth had occurred. On April 26 the patient entered the hospital with the first manifestations of toxemia and the characteristic hormonal imbalance which has been found to accompany the onset of symptoms. During the next two weeks she received 5 mg. of estradiol benzoate and 25 mg. of testosterone propionate daily. There ensued not only a depression of serum

TABLE IV. DIABETES, INCIPIENT PRE-ECLAMPSIA, HORMONAL TREATMENT

Mrs. A. R.,* aged 34 years, gravida ii (pre-eclampsia and stillbirth with first pregnancy), last catamenia Sept. 3, 1937. Due June 10, 1938.

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C. C. G.†	SERUM R.U./100 C.C. ESTRIN	URINE—24-HOUR EXCRETION PREGNANEDIOL MG.	ESTRONE R.U.	ESTRONE MG.	ESTRADIOL R.U.	ESTRADIOL M.G.	ESTRIOL R.U.	ESTRIOL MG.	PARENTERAL INJECTIONS ESTRADIOL MG.	PARENTERAL INJECTIONS TESTOSTERONE PROPIONATE MG.	CLINICAL NOTES B.P.	CLINICAL NOTES ALB.	CLINICAL NOTES EDEMA
4/26/38	33½	500	50	31	0		2,000	0.10	20,000	10.0			110/80	SPT	+
													Gained 10 lb. in 2 weeks. Abdl. pain; headache		
4/27/38											3.6 daily	25 daily			
5/ 3/38	34½	100	100	39	1,000	0.67	5,000	0.25	30,000	15.0			110/70	SPT	0
5/10/38	35½	50	75	64	2,500	1.68	5,000	0.25	60,000	30.0			110/60	0	0
													No further weight gain		
5/11/38													Delivery by cesarean section; baby lived		

*Ref. 18, Case 29.
†C. G., chorionic gonadotropin.

chorionic gonadotropin but also a rise in estrogens of both serum and urine and a shift in the distribution of urinary estrogens pointing to more conversion and less destruction—changes signifying more progestin. There was also a marked increase in urinary pregnanediol (from 31 to 64 mg. in 24 hours). Since it is unlikely that this rise could be entirely attributed to conversion of testosterone into progestin in the body, we are inclined to the opinion that it protected progestin against destruction, thereby enhancing the effectiveness of such amounts as were being elaborated. (The investigations of Pincus and Werthessen[17] and unpublished experiments in this laboratory have given evidence that substances chemically related to the female sex steroids enhance their action, apparently through slowing down the rate of their destruction.) Albuminuria and edema disappeared coincident with the establishment of a normal hormonal balance. A viable child was delivered by cesarean section. The patient was never sick enough to allow deductions as to the clinical effect of treatment, although, considering her previous history, an unfortunate outcome may have been averted.

In the case of Mrs. G. K. (Table V), injections were started as a preventive measure* five weeks after the first finding of excessive serum chorionic gonadotropin and before there was any suggestion of toxemia clinically, other than headache. At the time treatment was begun serum chorionic gonadotropin had increased still further, serum estrogen had failed to rise with advancing gestation and the urinary assays reflected low levels of both progestin and estrogens. Estrone was still present, however, signifying that the striking shift in estrogen metabolism, with complete absence of urinary estrone, which has been found to

*The assumption that an abnormal rise in serum chorionic gonadotropin during the fifth, sixth, or seventh month of pregnancy predicts later trouble is based on the study of serum chorionic gonadotropin in 173 pregnant women (31 of them diabetics).[5] Among the 83 cases with high chorionic gonadotropin there were no normal pregnancies, 90 per cent of these having been diagnosed as pre-eclamptic or eclamptic and 10 per cent having delivered prematurely. The incidence of premature delivery (rather than pre-eclampsia) in the high chorionic gonadotropin group was considerably higher among the diabetics (23.5 per cent) than among the nondiabetics (6 per cent).[5]

TABLE V. THREATENED, THEN INCIPIENT, PRE-ECLAMPSIA, HORMONE ADMINISTRATION

Mrs. G. K.,* aged 16 years, diabetic, gravida i, last catamenia Aug. 15, 1937, due May 22, 1938

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C.		URINE—24-HOUR EXCRETION							PARENTERAL INJECTIONS		CLINICAL NOTES		
				PREGNANEDIOL MG.	ESTRONE		ESTRADIOL		ESTRIOL		ESTRADIOL	TESTOSTERONE PROPIONATE	BLOOD PRESSURE	ALBUMIN‡	EDEMA
		C. G.†	ESTRIN		R.U.	MG.	R.U.	MG.	R.U.	MG.	MG.	MG.			
1/15/38	22	100											110/60	0	0
2/15/38	26½	200											110/80	0	0
3/ 1/38	28½	333	33										124/80	0	0
3/15/38	30½	500	33	30	500	0.33	500	0.025	4,000	2.0			124/90	0	Headache 0
3/22/38	31½	500	33	35	700	0.47	600	0.03	5,000	2.5	3.6 Daily	0	118/90	0	Headache +
3/23/38					2,000 (Estrone + Estradiol)				5,000	2.5		0			
3/24/38				24	500	0.33	1,500	0.075	4,000	2.0		0	116/50	0	0
3/25/38	32	200	33	23	2,000 (Estrone + Estradiol)				5,000	2.5		25 Daily			
3/27/38		100	50		1,000	0.66	2,000	0.10	6,000	3.0			110/70	SPT	0
3/28/38				26	3,000 (Estrone + Estradiol)				7,500	3.75					
3/29/38	32½				4,000 (Estrone + Estradiol)				7,500	3.75					
3/31/38		100	66	34	1,500	1.0	1,500	0.075	10,000	5.0	7.2 Daily	25 Daily	140-150/100-120	ST/T	Headache
4/ 6/38	33½	50	75	38	2,000	1.33	2,000	0.10	12,500	6.25			110-150/80-90	SPT	0 Headache
4/ 8/38											3.6 Alt. days	25 Alt. days	120/80	SPT	0
4/10/38	34			29	700	0.47	1,300	0.065	10,000	5.0			120/80	SPT	0
4/14/38				23	4,000 (Estrone + Estradiol)				10,000	5.0					
4/18/38	35	100	50	29	1,000	0.66	2,000	0.10	7,500	3.75			100/60	SPT	0
4/20/38		200	50	18	5,000 (Estrone + Estradiol)				7,500	3.75					Headache
4/26/38	36			21	1,000	0.66	3,000	0.15	7,500	3.75	0	25 Daily	100-120/70-80	SPT	0
4/30/38				6	500	0.33	4,000	0.20	6,000	3.0	7.2 Daily	25 Daily	100-120/60-80	SPT	0
5/ 3/38	37	200	100	6	3,000 (Estrone + Estradiol)				7,500	3.75			110/90	SPT	0
5/ 5/38				13	3,000	2.0	3,000	0.15	15,000	7.5			110/80	0	0
													Cesarean section. Baby lived.		

*Ref. 18, Case 28.
†C. G., chorionic gonadotropin.
‡SPT. slightest possible trace.

accompany clinical signs, had not yet taken place. Three days of estradiol benzoate alone (5 mg. daily) lowered the serum chorionic gonadotropin but had no effect on serum estrogen or on estrogen excretion other than to increase the estradiol. It appears that none of the injected estrogen was being converted and most of it was being destroyed. The excretion of pregnanediol decreased during this period. The giving of testosterone propionate with estradiol benzoate brought about an almost immediate change in the endocrine picture, and twelve consecutive days of this treatment were accompanied by a steady rise in serum estrogen and in urinary estrone, estriol, and pregnanediol. As in the preceding case (Table IV), the greater excretion of pregnanediol suggests that testosterone, in the amounts and for the period given, exerted a conserving influence upon progestin, thereby enhancing its action.[17] It is conceivable also that testosterone had a direct effect of its own, supplementing that of progestin, in the protection of the estrogens and in the conversion to estriol. On March 31, after six days of both testosterone and estradiol, the patient began showing clinical evidence of pre-eclampsia. Did this occur in spite of or due to prophylactic therapy or would it have been more severe without therapy? Clinical improvement was apparent one week later. Was it related to doubling the dose of estradiol and the ensuing further change in the hormonal balance in the direction of normal? From April 10 on, two paradoxes became evident in the chart for which we believe the continued administration of testosterone must have been responsible. The first is the alarming decrease in urinary pregnanediol. The second is the failure of total urinary estrogen to decrease strikingly and of estrone to disappear, as would be expected with such marked evidence of progestin lack. Inasmuch as continued injections of testosterone inhibit ovarian activity experimentally[16] and in women,[12] its prolonged administration, forty days, in this case would seem to have suppressed progestin production. It probably suppressed estrogen production also, but this effect would appear to be masked by the injections of estradiol and possibly testosterone's protective influence against estrogen destruction. Furthermore, testosterone was apparently fairly satisfactorily substituting for progestin in the conversion of estrone to estriol; in other words, it was maintaining a proper metabolism of the estrogens. During this period gestation progressed essentially normally and was terminated by elective cesarean section. The infant did well. In this case also no conclusions may be drawn as to the clinical effect of hormone administration, except that it did no obvious harm. Considering the fact that the patient was a juvenile diabetic and a primigravida, whose serum chorionic gonadotropin increased abnormally in the second trimester and who had incipient toxemia clinically for a few days, we are inclined to think that treatment may have prevented an accident to mother and/or child.

Because of its apparent inhibitive influence on the output of progestin when given for more than two weeks, we have avoided, at least for the present, the use of testosterone in further clinical trials. Moreover, it might be potentially harmful to fetus and mother in large dosage, because of its androgenic nature, although there was no evidence of such an effect in the case just reviewed.

Mrs. L. W. W. (Table VI), a diabetic since early childhood, was also treated before the development of any clinical evidence of toxemia on the basis of an abnormal rise in serum chorionic gonadotropin late in the sixth month (see footnote, page 413). Her first pregnancy had terminated in a stillbirth at seven months. At the time injections were started, the only demonstrable abnormality, aside from the excessive chorionic gonadotropin, was the fact that there had been no appreciable increase in estrogen excretion for eight weeks. Toward the end of a seventeen-day period of daily injections of estradiol benzoate (5 mg. daily) and progesterone, there was an increased excretion of pregnanediol and a good increase in estriol. Serum chorionic gonadotropin was still high, however,

TABLE VI. THREATENED PRE-ECLAMPSIA OR PREMATURE DELIVERY—HORMONE ADMINISTRATION

Mrs. L. W. W.,* diabetic, aged 25 years, gravida ii (stillbirth at seven months two years ago), last catamenia Aug. 15, 1937, due May 22, 1938.

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C.		URINE—24-HOUR EXCRETION								PARENTERAL INJECTIONS		CLINICAL NOTES		
		C. G.†	ESTRIN	PREGNANEDIOL MG.	ESTRONE R.U.	ESTRONE MG.	ESTRADIOL R.U.	ESTRADIOL MG.	ESTRIOL R.U.	ESTRIOL MG.		ESTRADIOL MG.	PROGESTERONE MG.	BLOOD PRESSURE	ALB. GM./24°	EDEMA
11/ 5/37	12	100		7.0	120 (Estrone + Estradiol)				400	0.2				110/60	0.278	0
12/14/37	17	50		18.6	700 (Estrone + Estradiol)				3000	1.5				110/70	0.408	0
1/18/38	22	100	25	0?‡	2,500 (Estrone + Estradiol)				10,000	5.0				110/80	0.768	0
2/ 8/38	25	200	33													
2/28/38	28	200	33	89	1,000 (Estrone + Estradiol)				15,000	7.5				110/60	0	0
3/14/38	30	300	33	93	1,300	0.87	2,700	0.133	10,000	5.0				120/60	0.168	0
3/19/38		300	33	103	1,700	1.14	3,300	0.165	15,000	7.5		3.6 daily	10 daily			
3/20/38	31				1,700	1.14	3,300	0.165	15,000	7.5		↓	↓	106/80	0.132	0
3/21/38				95	3,000	2.0	4,500	0.225	15,000	7.5						
3/22/38					2,000	1.33	3,000	0.15	15,000	7.5						
3/23/38	31½			85	5,000 (Estrone + Estradiol)				12,000	6.0						
3/27/38	32	200	50	101	1,700	1.14	3,300	0.165	20,000	10.0				110/60	0.551	0
4/ 2/38	33			113	4,000	2.67	4,000	0.20	20,000	10.0		↓	↓			
4/ 6/38	33½	200	50	121	1,200	0.80	2,800	0.14	40,000	20.0		0	20	120/80	0.325	0
																Uterine cramps
4/ 8/38	34			100	3,500	2.33	4,000	0.20	30,000	15.0		↓	↓	110/80	0.121	0
																Uterine cramps
4/14/38		300	50	77	4,500	3.0	3,000	0.15	30,000	15.0		7.2 daily	20 daily	110-130/60-80	0.360	0
																Uterine cramps
4/20/38	35½	100	50	39	2,500	1.66	7,500	0.375	40,000	20.0				120-130/60-90	0.405	0
																Uterine cramps
4/23/38	36	100	75	89	2,500	1.66	7,500	0.375	80,000	40.0				110-120/70-80	0.474	0
4/25/38				110	15,000 (Estrone + Estradiol)				80,000	40.0						
4/27/38					5,800	3.85	7,500	0.375	80,000	40.0				120-130/80	0.760	0
4/28/38	36½											↓	↓	Cesarean section. Baby lived		

*Ref. 18, Case 34.

†C. G., chorionic gonadotropin.

‡See footnote Table III.

and serum estrogen had not been augmented as much as would have been anticipated. In Table V it is observed that 5 mg. of estradiol benzoate were barely adequate for depressing serum chorionic gonadotropin. The omission of estradiol injections for eight days because of uterine cramps was followed, not only by a rise in serum chorionic gonadotropin, but also by a lowering of urinary pregnanediol and reduced conversion of estrone to estriol, despite the fact that progestin-administration had been doubled. (Incidentally, uterine cramps became more severe.) These observations carry the important implication that parenterally-introduced progestin alone is no more effective than estrogen alone in re-establishing a normal balance once the progestin-deficient metabolism of the estrogens has become established. It appears that adequate estrogen is required for the proper metabolism of progestin (through protecting it from destruction and aiding its conversion to pregnanediol), just as progesterone protects estrogen and facilitates estrone to estriol conversion. The fact that the omission of estradiol resulted in such marked hormonal changes implies that the previous amounts of estrogen had been barely adequate, and that, had the patient received no injections, a progressive imbalance might have occurred. These points are emphasized by the shifts consequent upon the administration of estradiol in double dosage as well as progesterone—normal chorionic gonadotropin, increased serum estrogen and greater urinary pregnanediol and estriol. Although coincident with this establishment of a normal balance, uterine cramps ceased, no committal can be made as to clinical benefit in this case.

Mrs. R. M. (Table VII) had not been followed by us prior to the onset of pre-eclampsia. On January 5 blood was taken for assay, the patient having gained seven and one-half pounds in one week and in that time having developed edema, albuminuria, and an elevated blood pressure. Serum chorionic gonadotropin was high and serum estrogen low. One week of magnesium sulphate catharsis and water and salt restriction reduced the edema but had no effect on blood pressure or albuminuria. A twenty-four-hour urine before the initiation of hormonal therapy contained considerably less estriol than is normal for the last month of pregnancy and no estrone. Pregnanediol excretion was within the limits of normal, but an actual deficiency of progestin was nevertheless indicated if our hypothesis is correct that the proper metabolism of the estrogens is dependent upon sufficient progestin. Furthermore, it seems probable that both pregnanediol and estrogen excretion were rapidly decreasing when injections were started. This is indicated by the urinary findings during the first days of treatment, namely, the small increments in pregnanediol, the drop in estriol, and the fact that the only increase in urinary estrogen was in estradiol, the administered hormone. Eight days of treatment were followed by the establishment of a normal estrogen and progestin balance and unquestionable clinical improvement. Neither of these changes was definitely apparent until after the sixth day of treatment. On the third day after injections were stopped the urinary assays still revealed a normal metabolism of the hormones, although the estrogens had dropped to a lower level. The only clinical change was a slight rise in blood pressure. By the fourth day without injections, however, albuminuria had increased and edema was present. Hormone quantification covering the next two days revealed elevated serum chorionic gonadotropin, a falling off of serum estrogen and changes in the urinary constituents which reflected decreased conversion and greater destruction of estrogens due to progestin-deficit. Pregnanediol and total estrogens were lower at this time than they had been two weeks earlier, due probably to decreasing elaboration as well as greater destruction. The patient's signs became more severe and labor was induced.

This case, in which clinical and endocrine changes are so closely related, supplies our most persuasive evidence that a progestin-deficient metabolism of the estrogens is directly concerned in pre-eclampsia. It also is the only case in which toxemia was sufficiently pronounced to warrant the conclusion that amelioration resulted from therapy with

TABLE VII. NONDIABETIC, PRE-ECLAMPSIA, HORMONE ADMINISTRATION

Mrs. R. M., aged 26 years, gravida i, last catamenia April 25, 1938, due Jan. 31, 1939.

DATE	WEEKS PREGNANT	SERUM R.U./100 C.C.		URINE—24-HOUR EXCRETION						PARENTERAL INJECTIONS		CLINICAL NOTES				
		C. G.*	ESTRIN	PREGNANEDIOL MG.	ESTRONE R.U.	ESTRONE MG.	ESTRADIOL R.U.	ESTRADIOL MG.	ESTRIOL R.U.	ESTRIOL MG.	ESTRADIOL MG.	PROGESTERONE MG.	BLOOD PRESSURE	ALBUMIN QUAL.†	ALBUMIN GM. 24°	EDEMA	MISCELLANEOUS
12/29/38													130/80	0		0	Weight 152½ lb.
1/ 5/39	36½	500	33										140/90	T		++	Weight 160 lb.
1/11/39													140/90	T		0	After 1 wk. $MgSO_4$ + water and salt restriction
1/12/39	37½	500	33	76.4	0		2,700	0.13	20,000	10.0			140/90	LT	2.3	0	
1/13/39											7.2 daily	50 daily					$MgSO_4$ reduced. Water intake
1/14/39				81.0	0		10,000	0.50	4,000	2.0			138/88	T	1.8	0	increased to
1/15/39													140/85-90	T	2.7	0	2,000 c.c. daily
1/16/39				88.6	6,700	4.45	13,300	0.66	13,300	6.6			125-130/85-90	T	2.8	0	—to delivery
1/17/39													130/90	T	1.6	0	
1/18/39				107.0	6,700	4.45	13,300	0.66	15,000	7.5			130/95	T	1.5	0	
1/19/39	38½												130/90	ST	1.1	0	
1/20/39													130/90	ST/T	1.1	0	
1/21/39				95.0	6,700	4.45	13,300	0.66	53,000	26.5			120/80	ST	1.1	0	
1/22/39		50	100								0	0					
1/23/39													120/85	ST/T	1.1	0	
1/24/39				101.0	1,300	0.86	4,000	0.20	40,000	20.0			135/85-90	T	1.1	0	
1/25/39													135/90	T	1.6	+	
1/26/39	39½	100	50	60.0	3,400	2.25	6,600	0.33	13,300	6.6			135/90	T	2.6	+	Castor oil + enema in P.M.
1/27/39		200	<33		2,000	1.34	8,000	0.40	10,000	5.0				LT	5.5	++	Labor and delivery. Baby lived

*C. G., chorionic gonadotropin.

†T, trace; ST, slight trace; LT, light trace.

large but perhaps still barely adequate doses of hormones. This conclusion is confirmed by the recrudescence of toxemia on the cessation of treatment.

DISCUSSION AND SUMMARY

The previously published hypothesis[4] concerning the metabolism of estrogens in women involves the assumption that estradiol is the primary estrogen. Experimental results[4, 6, 7] have indicated that estradiol is convertible into estrone, this reaction being reversible, and that estrone is convertible into estriol, this reaction being irreversible and greatly facilitated by the action of progestin. Progestin has also been found to protect estrogens against destruction. The above hypothesis has been considerably strengthened and enlarged upon by the data herein presented.

Throughout these studies of pregnant women progestin has appeared to facilitate the utilization and metabolism of the estrogens through enhancing conversion to estriol and diminishing destruction. The most convincing evidence for this effect of progestin is found in the following: administration of estradiol benzoate alone brings about very little increase in excretion of estrogen and most of that in the estradiol fraction. When progesterone and estradiol benzoate are given, estrogen excretion is further augmented and most of the increase is found in the estriol fraction.

Estradiol is usually found amplified at times when total estrogen is lowered, i.e., when there is greater destruction associated with less conversion of estrone to estriol. The data are in keeping with the assumption that this factor is an estrone-precursor and that the estradiol to estrone reaction is a reversible one, the rate and direction of which are dependent (law of mass action) upon the rate of the irreversible estrone to estriol conversion. The sudden disappearance of estrone from the urine, in the face of continued or increased excretion of estradiol, has been taken to signify reversal of the estradiol to estrone reaction and more rapid destruction of all the estrogens. In this situation, which, in pregnancy, has been encountered only at spontaneous labor and at the onset of clinical signs in toxemia, estriol is still found in the urine, although in reduced amounts. Since estriol is probably formed from estrone, our only explanation for the disappearance of the latter is that, being chemically more labile than estriol and ordinarily present in much smaller amounts, any of it which escapes destruction and is not converted to estriol or back to estradiol is too little to be demonstrable. The fact that estriol is always found in pregnancy urine carries the implication that progestin is never completely absent.

That low values for urinary estrone and estriol may be accountable to renal retention seems to us untenable, both because of the failure to find a concomitant increase of serum estrogen and because a selective kidney retention as regards estrone and estriol and not estradiol seems most unlikely. There is considerable evidence in the data presented that low values for estrogens are not entirely due to decreased conversion and more rapid destruction, but that this finding is partly accountable to a decreased elaboration of estrogen as well as progestin.

Whether the urinary values for sodium pregnanediol glucuronidate may be accepted as an accurate gauge of progestin elaboration is open to question. Since this substance is measured in its combined form, a failure of conjugation or some unusual hydrolysis after it had passed the kidney tubules might account for low values. This latter possibility has been exemplified by the occasional absence of sodium pregnanediol glucuronidate in the urine of a woman whose excretion of this material was otherwise following a consistent curve (Tables III and VI). Low levels of pregnanediol from failure of conjugation or kidney retention in pre-eclampsia may be ruled out, since an actual deficiency of progestin is reflected by the distribution of the urinary estrogens. Aside from decreased production of progestin, there are two other possible causes for low urinary pregnanediol glucuronidate: (1) failure of conversion of progestin to pregnanediol and (2) destruction of secreted hormone.

It seems quite likely that conversion to pregnanediol may represent physiologic utilization of progestin, just as the estrone to estriol conversion appears to play an important part in the utilization of estrogens. Administration of progesterone without a commensurate recovery from the urine of pregnanediol would suggest inadequate physiologic utilization as well as destruction. The fact that injection of progesterone alone results in less pregnanediol excretion and less estrone to estriol conversion than follows the injection of progesterone and estrogen (see Table VI) indicates that estrogen facilitates the conversion of progestin to pregnanediol and prevents destruction just as progestin facilitates estrone to estriol conversion and prevents estrogen destruction. These metabolic considerations are entirely in accord with the many experimental studies which have shown the complementary effect of estrogen and progestin on one another in their physiologic activities.

One of the questions which our studies have thus far failed to answer is how much of a given decrease of estrogen and progestin is due to incomplete metabolism with destruction and how much to reduced elaboration. Any deficiency which precedes the marked change in the partition of urinary estrogens which accompanies the onset of clinical signs is presumably accountable to decreasing elaboration. The suggestion that chorionic gonadotropin is utilized in the production of these steroids and that its abnormal rise signifies failure of such utilization is proposed merely as a working hypothesis. Observations commented upon in the presentation of results seem to support this hypothesis. Once the deficiency of progestin and estrogen is established, the destructive mechanism probably accounts largely for the abnormally low values as well as the deranged metabolism observed when toxemia is present. That the deranged metabolism is associated with rapid destruction is well demonstrated by the failure, after hormone administration, to find any immediate increases, in serum or urine, commensurate with the amounts introduced. Continued injections, however, have been followed not only by a more normal metabolism of estrogen and progestin but also by less rapid destruction, as indicated by the greater recovery of the injected hormones.

In fact, it will be observed that the prolonged administration of these substances has been followed in most instances by a greater recovery of urinary estrogen and pregnanediol than accountable to the materials administered. Greater elaboration of estrogen and progestin with advancing pregnancy is, of course, to be expected under normal conditions. There is considerable evidence in the data presented, however, that the reverse situation follows an abnormal rise in serum chorionic gonadotropin after the fifth month. The lowered serum chorionic gonadotropin after hormone administration together with the evidence for increased elaboration of estrogen and progestin upon prolonged treatment, suggests a more efficient utilization of chorionic gonadotropin because of the injected steroids.

In the 2 cases in which testosterone propionate had been substituted for progesterone, a number of interesting possibilities were revealed concerning the effect of this hormone upon estrogen and progestin metabolism. That estrogens were being more completely metabolized and less rapidly destroyed, when testosterone was given together with estradiol, than when estradiol alone was administered, was definitely shown. During the first two weeks of therapy this appeared to be the result of a higher level of progestin, due either to more elaboration or less destruction of progestin because of the injected testosterone. The continued administration of testosterone was accompanied by a marked falling off of urinary pregnanediol, but by evidence, based on the amounts and partition of urinary estrogens, for a continued satisfactory metabolism and utilization of the estrogens. From these observations it would appear that testosterone has a direct effect similar to that of progestin upon estrogen metabolism, that it may protect progestin as well as estrogen against destruction, but that its prolonged administration suppresses the elaboration of progestin (and probably estrogen also, an effect which would have been masked in these 2 cases by the parenterally-introduced estrogen). These properties of testosterone may well explain its apparent efficacy in the treatment of such conditions as functional flowing.[16]

The results reported establish pretty conclusively that a progestin and estrogen deficiency pertains in late pregnancy toxemia and accounts for the

deranged metabolism of these 2 steroids which is found to accompany the onset of clinical signs. They also demonstrate that a more normal endocrine balance may be accomplished by replacement therapy, provided injections are started sufficiently early in the course of the disturbance, are given in large amounts and continued for a fairly prolonged period, at least one week. Interruption or discontinuation of therapy has been followed by a reversal of the hormone changes. In none of the treated patients, except for Mrs. R. M. (Table VII), were clinical signs sufficiently severe to exclude the possibility that clinical improvement might have occurred without therapy. On the other hand, there appears to be a correlation between clinical and hormonal changes. In the case of Mrs. R. M. (Table VII), such a correlation was especially apparent and the evidence in this case alone is perhaps sufficient to warrant the conclusion that some alteration associated with a deranged metabolism of estrogen and progestin due to a deficiency of both is directly concerned in the clinical signs of pre-eclampsia. The fact that an entirely similar hormonal picture is found at the time of normal delivery sheds some light on the mechanism of spontaneous labor and leads us to wonder why premature delivery, at the time toxic signs first appear, is not as common among nondiabetics as it seems to be among diabetics.

CONCLUSIONS

A rise in the gonadotropic potency of the serum after the fifth month of pregnancy is followed by a decreasing production of progestin and of estrogen. Such a phenomenon may reflect a decreasing utilization of the pregnancy gonadotropic factor for the elaboration of estrogen and progestin. The deficiency of these 2 steroids results in a deranged metabolism of both, involving less complete conversion and utilization and more rapid destruction. Such a shift in steroid metabolism pertains at the onset of normal labor. When this change occurs prior to term, it is accompanied by the clinical signs of pre-eclampsia (or by premature delivery).

Because of the more rapid destruction which accompanies the mutual deficiency of progestin and estrogen, and because of the fact that each of them, in adequate amounts, is required for the proper metabolism of the other, a re-establishment of a normal hormonal balance by replacement therapy can only be accomplished by the continued injection of both of them in large amounts. There is evidence that clinical improvement accompanies the establishment of a normal balance.

Testosterone propionate has an effect similar to that of progestin upon the metabolism of the estrogens. It also appears to protect both estrogen and progestin against destruction. It is perhaps not a satisfactory substitute for progestin in pre-eclampsia, however, because its prolonged administration apparently suppresses the elaboration of progestin (and possibly estrogen) and may have other undesirable effects due to its androgenic nature.

The administration of progestin and estrogen as a therapeutic measure* in pre-eclampsia is as yet of very limited clinical value for three reasons: (1) the large amounts required are not commercially available in sufficiently concentrated form and are still too costly; (2) in the amounts and kinds administered in this study, injections must be con-

*This form of therapy has appeared to reduce infant mortality in a small series of diabetic pregnancies treated at our instigation at the New England Deaconess Hospital.[18] The hormone assays on most of these patients were performed by us and treatment advised only in those showing an abnormal rise in serum chorionic gonadotropin between the fifth and seventh months.

tinued for at least six days before any effect upon the hormonal or clinical picture can be expected. In fulminating pre-eclampsia such a delay is not justifiable. (3) The indications are that in cases of greater severity than any herein reported, in which estrogen and progestin destruction may be even more rapid, replacement therapy would be of no avail.

The principal value of the data presented lies in the added light which has been shed upon hormonal interrelationships in pregnant women and in the intimation that the primary etiology of pre-eclampsia, eclampsia, and certain cases of premature delivery may be associated with the premature development of an hormonal situation entirely similar to that which precedes normal delivery.

ADDENDUM

Since this paper was submitted for publication, 11 additional cases of pre-eclampsia have been studied; only 3 of them are diabetic. All of the 8 nondiabetic patients were exhibiting more pronounced toxic signs than any of the cases reported above, and in each, the urinary findings reflected a marked deficiency, together with the characteristically abnormal metabolism of estrogen and progestin. Five of them received estrogen and progestin (10 mg. estradiol benzoate and 30 to 50 mg. progesterone daily). Two showed definite clinical improvement and a more normal steroid metabolism during hormone administration, although neither of them was "cured." The other three patients, one with severe fulminating pre-eclampsia and two in whom clinical manifestations had been of four to six weeks' duration before treatment, were only temporarily benefited and then gradually became worse in spite of continued hormone administration. In both untreated and treated cases, the clinical and hormonal changes ran parallel. The data covering these patients will be published later.

The study of the diabetic cases in this report was facilitated through the essential and deeply appreciated cooperation of Dr. Priscilla White of the George F. Baker Clinic of the New England Deaconess Hospital, Boston, who followed our specifications in the administration of the materials used in therapeutic trials, supervised the collection of specimens and supplied us with clinical data. These same cases are included in a clinical study by her and others.[18] To Dr. Weston Sewall, Boston, we are indebted for helping us to acquire the data in Table VII. The Schering Corporation, through the cooperation of Dr. Erwin Schwenk, supplied the large quantities of hormones used, some of them specially prepared. Miss Sara Schiller gave much necessary technical assistance.

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SUPRAVESICAL EXTRAPERITONEAL CESAREAN SECTION*

Presentation of a new technique

Edward G. Waters, M.D., F.A.C.S., Jersey City, N. J.
(From the Margaret Hague Maternity Hospital.)

THE purpose of this paper is to present a new technique for a true extraperitoneal performance of cesarean section. To avoid confusion in terms and to clarify the issues involved, the present-day cesarean techniques are first considered. I would recall the early need for extraperitoneal operation, based upon the inadequate asepsis and antisepsis, poor or no anesthesia, imperfect technique, and other important factors in former days; likewise, the high incidence of neglected cases, with previous unsuccessful attempts at vaginal delivery. In the present century, and more especially the past twenty-five years, the fruits of bacteriologic, anatomic, and surgical research have made all abdominal operations, including cesarean sections, incomparably safer than before. The advances in all fields have effected such reductions in mortality and morbidity that cesarean section mortality in good clinics does not exceed 5 per cent as compared to 50 to 100 per cent in the nineteenth century. The question might therefore be asked: Are true extraperitoneal cesarean sections needed today? Before arbitrarily answering, a consideration of the purpose of the operation is in order.

The low transperitoneal retrovesical operation is by all standards safer and better than the low segment Sänger incision, but it cannot and does not prevent peritoneal contamination. Cesarean hysterectomy cannot conceivably be better than a true extraperitoneal operation except in the 15 to 20 per cent group of fatal sepsis through uterine wall and lymphatics, and even in this group one may question its effectiveness. It is obvious that, if its indications are broad, a large majority of the operations are needless sacrifice of uteri, while, if the operation is long delayed, it will be ineffective for the very indication it is presumed to satisfy. The indication for a true extraperitoneal operation is therefore the probable or actual existence of intrauterine infection. If properly done, it should largely remove peritonitis as a cause of postoperative mortality, and at the same time it conserves the uterus.

It logically follows that the operation should be done in cases of reasonable doubt, if its technical safety and the results obtained in any appreciable series can be demonstrated as not more hazardous than other cesarean techniques. The results obtained with the Latzko procedure by Burns, Steele, Norton and others give a mortality for a group of 151 cases as 5.3 per cent. This figure, considering the status of the majority of cases at the time of operation, compares very favorably with the transperitoneal operations.

*Presented before the New York Obstetrical Society, January 10, 1939, and in essentially the same form before the Brooklyn Gynecological Society, April 7, 1939, the Boston Obstetrical Society, March 21, 1939, and the New York Academy of Medicine, May 23, 1939.

It would seem that the results of the extraperitoneal operations, with uterus and the function of childbirth conserved for the patient, should relegate cesarean-hysterectomy to the group of out-dated and obsolete operations except in unusual instances.

The extraperitoneal operation of Latzko is not simple, neither is it too difficult for the obstetric surgeon. It does contain a number of real and potential dangers, however, which vitiate to some extent and in some hands, its acknowledged value.

The lateral dissection itself is not simple, and one without sufficient experience may encounter unexpected difficulties. Variations in degree of dextrorotation of the uterus, close proximity of the ureter with marked dextrorotation, varicosities in the broad ligament and bladder base, low and very adherent peritoneal fold, the relatively small exposure in deep pelves and in fat women, the likelihood of peritoneal laceration in extracting large babies, introduce threatening factors in the performance of any Latzko procedure.

Theoretically, the most highly desirable extraperitoneal operation would (1) avoid opening the peritoneum during or after extraction of the baby, (2) avoid injury to the ureters, (3) avoid injury to the bladder, (4) avoid the easily infected cellular tissue lateral to the bladder, (5) give full view of the separated tissue and the operative field, (6) give ample room for extracting any size fetus, (7) permit careful two-layer closure of uterus and thorough inspection for venous bleeding, if any, (8) leave the patient with a good uterine and abdominal wall.

The author considered the direct supravesical approach, with certain modifications, best suited to meet these desiderata. Operators for radical removal of the bladder have long denied, yet seemingly it is an accepted obstetric belief, that the supravesical peritoneum is very adherent. The peritoneum is extremely adherent to the perivesical fascia but both as a unit are separable from the bladder. It is then possible to identify the perivesical and periuterine portions of the fascia endopelvina, and by incising them in given manners and planes, permit adequate separation of the bladder from the uterus.

Once accomplished, these two maneuvers should permit the bladder to be dropped down and forward from the lower uterine segment, and the separated supravesical peritoneum with attached fascia and the periuterine fascia and peritoneum held upward, thus giving a large exposure of the lower uterine segment.

The ease with which this is done is dependent upon known and easily demonstrable changes in the pelvic structures induced by pregnancy. The uterine growth and displacement out of the pelvis loosens the peritoneal attachment to the lower uterine segment, whence it is separated with amazing ease. The lifting of the vesicouterine plica bares the bladder of peritoneum except for its posterosuperior surface, a spread of about 3 to 4 cm. in the collapsed state. The distention of the lower segment of the uterus and the thinning of the pericervical and pubovesical ligaments of the fascia endopelvina in the last trimester of pregnancy permit easy separation of the posterior surface of the bladder from the uterus and enables one to carry it far down and forward.

In actual dissection of the bladder peritoneum, the subperitoneal tissue is carried away with it, conserving its vitality and facilitating its postoperative reattachment.

If the uterus now be incised transversely, in a crescentic manner with apex downward, several effects are obtained. The curved incision, acting as the "diameter for the circular birth opening in the uterus," is more effective than a straight line between its terminal points could possibly be, for the longer line or diameter allows a larger "birth circle" in the elastic uterus. Again, by curving upward, it effectively escapes the uterine end of the broad ligaments, whether or not they are venously engorged. The easily infected cellular tissue low down at the bladder supports is avoided. Nothing is cut that is not under direct vision. The uterine arteries are avoided and the ureters cannot possibly be jeopardized, even in cases of marked dextrorotation of the uterus. The incision is kept for most of its length well within that section of the uterus where fibrous muscular ratio favors scar placement. Past experience with the incision in transperitoneal operations shows it to be an excellent one, and by all comparative data, the best site for a uterine scar.

DESCRIPTION OF OPERATION

With these concepts in mind, the author proposed and performed the following operation:

Patient is prepared vaginally. An indwelling catheter is placed in the bladder and connected with an irrigator containing sterile aqueous solution of methylene blue.

A left paramedian "trap door" incision is made in the abdomen from pubes to 1 inch below the umbilicus. In fat women and where desired, the Pfannenstiel incision is chosen. The bladder is distended with 200 c.c. or more of solution. Transversalis fascia is incised vertically. The laminated perivesical fascia is incised down to bladder muscularis for 1 inch about two-thirds of the distance to the bladder fundus. The vesical vessels are seen lying upon it as the handle of a scalpel is inserted and the fascia freed, and then incised transversely over the top and left of the bladder fundus in a "T" fashion. This permits the parietal peritoneum above the bladder to be carried up with the fascia, and the bladder separation begun. (The bladder is then drawn downward and the vesicouterine plica sought. The bladder is now emptied.) This is usually located at the left side of the bladder near the top, where the plica is most easily seen and the depth is less, due to the usual dextrorotation of the uterus. The areola tissue in this area is easily separated by holding the bladder down with a sponge and separating bluntly. Care must be taken to seek and identify the fold of peritoneum which in every case looks exactly like a hernial sac. When the "sac" is seen, direct division of the loose areolar tissue is permitted and (with the operator on the patient's right side) the finger of the left hand insinuated under it. Behind the finger is the perivesical fascia and the uterus, above the peritoneal fold, below the perivesical fascia at the back of the bladder and resting on the finger is the peritoneal fold of the uterovesical pouch. The integrity of the last must be maintained. This is the most important part of the entire operation.

By sharp dissection with knife tip and under direct vision it is now possible to free the vesicouterine plica from the posterior surface of the bladder. This involves incising again the perivesical fascia, but this time near the uterovesical junction. This permits the bladder to be dropped down and forward in back of the pubis. Any bleeding from retrovesical veins is directly visible and points are ligated with No. 00 plain catgut. A large curved angle retractor holds the bladder downward, and two Richardson's are used for lateral retraction. A central "nick" is made through the now well-exposed lower uterine segment about 1½ inches above the

depth of the bladder effacement, and cultures made from the amniotic fluid and uterine cavity. With a bandage scissors, a crescentic incision is then carried in either direction, first to left, then to right, the ends curved upward, and reaching 1 to 1½ inches above the apex of the crescent.

In vertex presentations, one blade of a forceps is slipped into place above the symphysis and used as a vectis to lift the head out of the pelvis. The head is delivered through the incision by use of the vectis and suprafundal pressure. The edges of the incision are seized with Allis or "T"-clamps, using four in all.

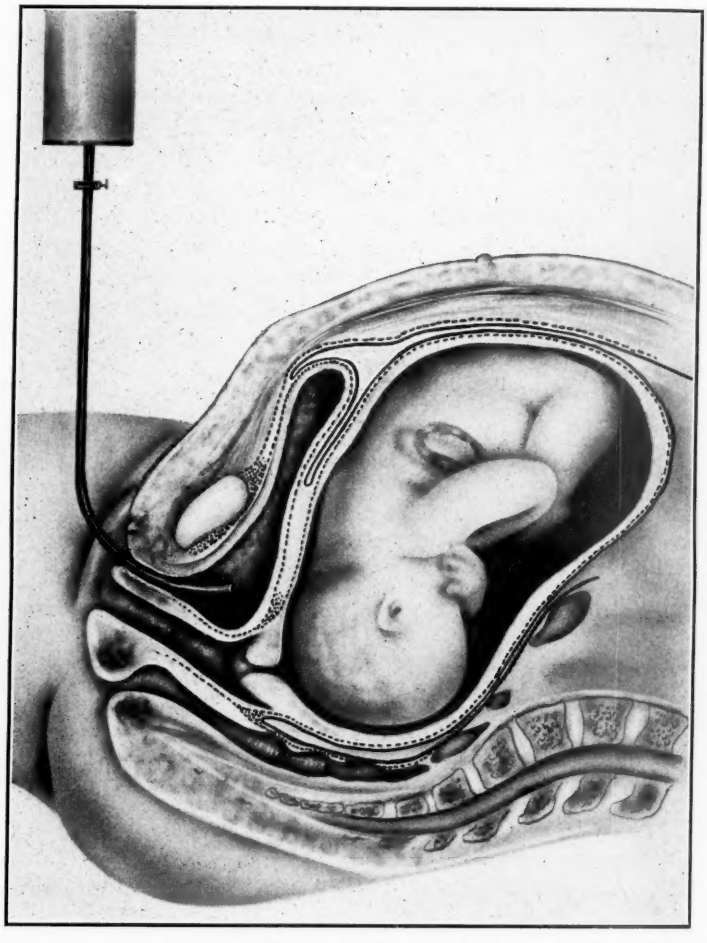

Fig. 1.—Diagrammatic cross section, showing perivesical and periuterine fascia and peritoneal relations. Outline of partially distended bladder shown, indicating depth of uterovesical peritoneal plica.

Suction clears the wound area. A running suture begins at the left side of the incision with stitches placed closely after the placenta is manually removed with its membranes. The second layer of sutures is a running Lembert, or Cushing, completely inverting the first, so that any wound infection will tend to discharge into the cervical segment and be cast out with the lochia.

The operative area is thoroughly cleaned, inspected for any venous ooze, and the bladder refilled to check for damage. It is then emptied, and the retrovesical space drained with rubber tissue. The transversalis fascia is sutured with interrupted chromic No. 1, and the rectus fascia with continuous chromic No. 2. Interrupted silk retention sutures and clips are used on the skin.

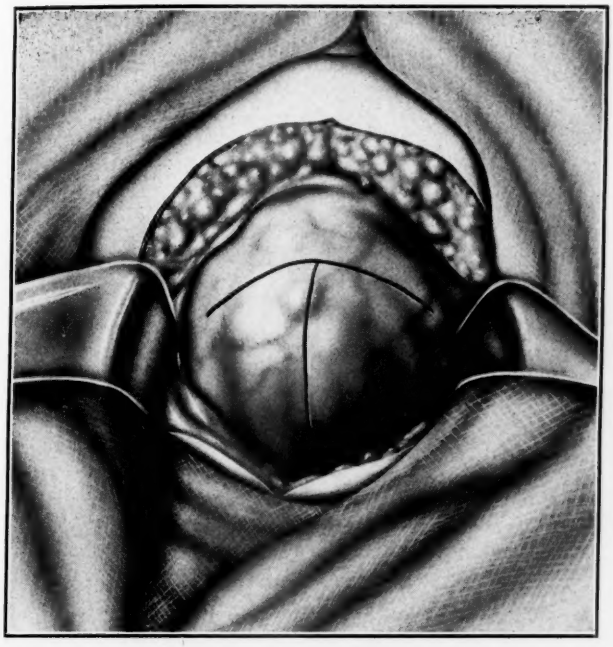

Fig. 2.—Distended bladder covered by perivesical fascia and the transversalis fascia below the parietovesical peritoneal fold. A "T"-shaped fascial incision made as indicated, down to the muscularis. This is determined by its character and by the vesical blood vessels lying between fascia and bladder muscularis. Dissection is done with knife, handle, and curved scissors.

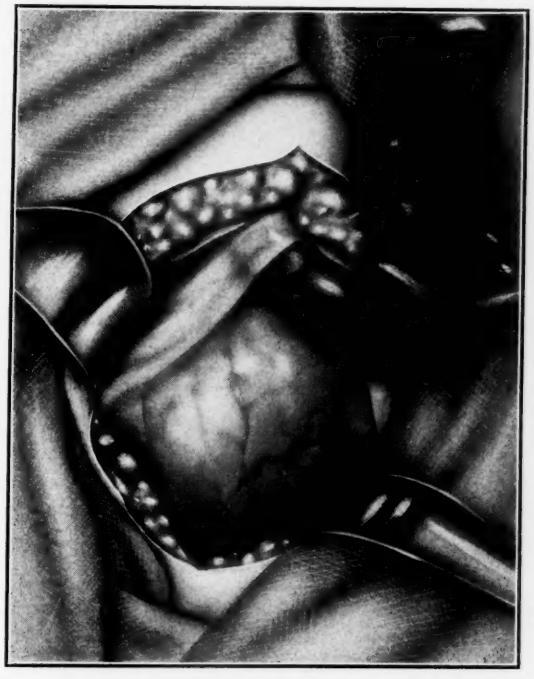

Fig. 3.—Fascia above top of "T"-incision dissected upward with finger, scalpel handle, and gauze. This denudes anterior and upper part of the bladder of its fascia and overlying peritoneum.

Certain minor variations in technique may be employed, depending upon the patient and the operator. The amount of bladder fill may vary from none to 400 or 500 c.c. Fascial identification is simpler with a well-filled bladder, but fascial dissection is easier and quicker with the bladder empty. The inserted catheter serves as a guide to bladder outline.

To briefly review the manner of fascial incisions, it is seen that first the transversalis fascia is incised. Then the perivesical fascia is divided as it covers the

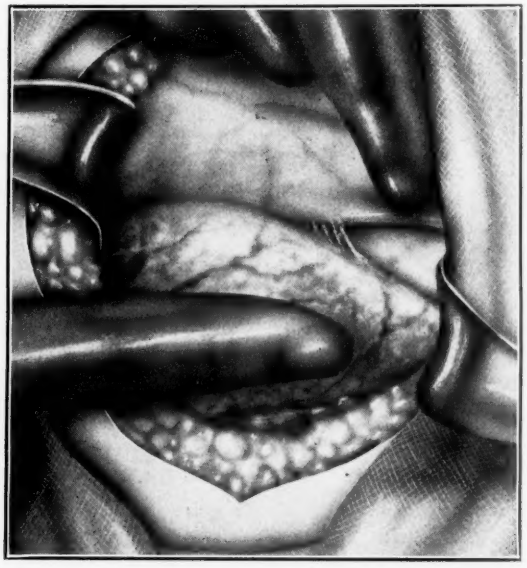

Fig. 4.—Approach over left top of bladder. Collapsed bladder drawn downward with gauze, the peritoneofascial tissue above "T"-incision drawn upward. Hernia-like margin of vesicouterine plica sought behind left top of bladder. Lower finger on bladder, upper on hernialike peritoneal margin, and between is noted lower anterior segment of uterus.

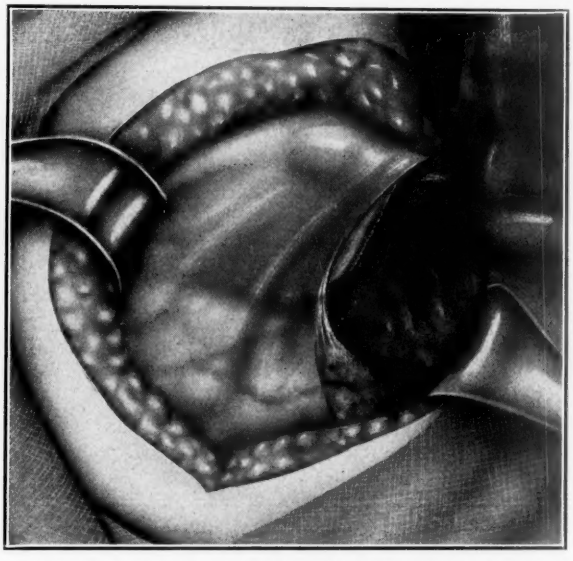

Fig. 5.—Plica with attached fascia partially lifted from anterior surface of uterus. Attachment of fascia to bladder fundus shown.

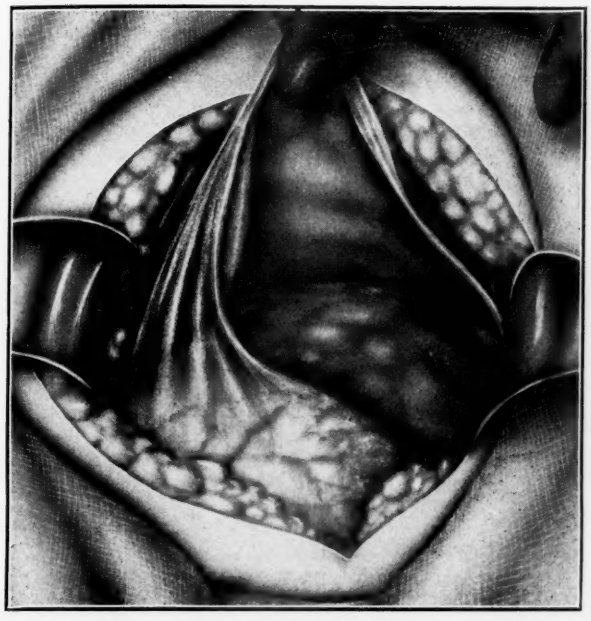

Fig. 6.—Plica well dislocated from bladder by sharp dissection, exposing larger section of uterus.

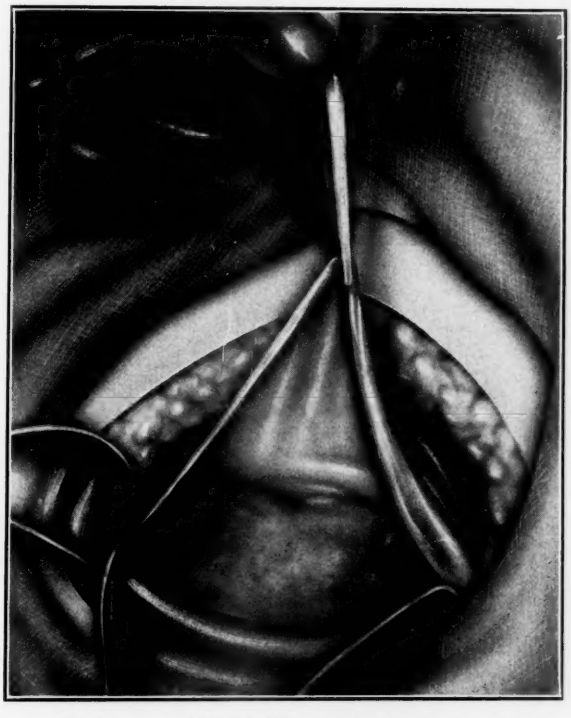

Fig. 7.—Plica completely separated, bladder retracted down with large curved retractor. (Forceps demonstrates mobility of plica.)

fundal portion of the bladder near the parietovesical peritoneal reflection. After separation of this, especially over the left upper bladder angle, the same layer is again incised posteriorly to expose the fascia covering the lower uterine segment. Thus the bladder is "denuded" of its fascia which remains attached to the peritoneum, from bladder fundus to the uterovesical pouch. This permits the peritoneum to be freely and easily lifted and the bladder dropped far down. Incision of the uterine fascia over the lower segment occasionally is needed to increase the mobility of the uterine peritoneum.

Postoperative Care.—The drain is left in 2 to 5 days, depending upon the infectivity of the case. The bladder catheter is left in two days. Prostigmin (P) is given every 4 hours for 24 hours; then every 6 hours for 24 hours. Spinal anesthesia is the anesthesia of choice, and patients are permitted fluids immediately, soft diet in 24 hours and regular diet in 48 hours, barring complications. Intravenous glucose with or without insulin and blood transfusions are freely resorted to where there is the slightest indication.

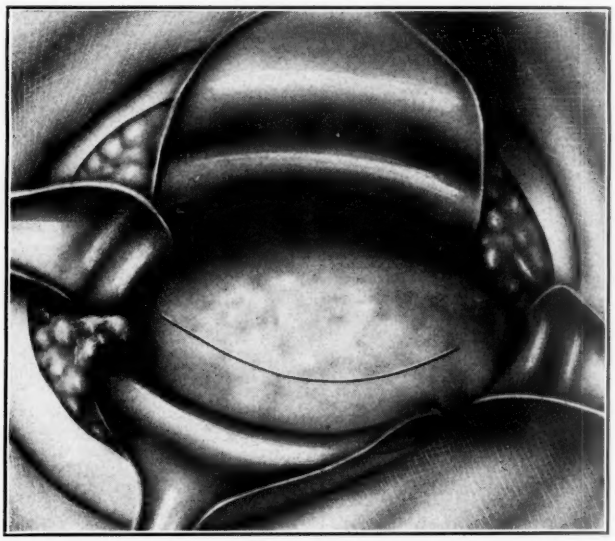

Fig. 8.—Retractors hold bladder down, peritoneofascial flap upward and also placed for adequate lateral exposure. Field shown is lower uterine segment. Type and location of uterine incision indicated.

RESULTS IN 32 CASES

Thirty-two patients have been operated upon by the technique described above. Two operators performed 27 out of the 32 operations listed.

Twenty-four of the patients were primiparas, 6 were multiparas. Of the latter, 3 had previous cesarean sections. There were no maternal deaths among the 32 cases.

There was one fetal death. This patient, a para iv, had ruptured membranes 71 hours and had been in labor 82 hours. Although her past obstetric experiences had been satisfactory, a pelvic operation of unknown type had preceded this pregnancy. The cervix became neither dilated beyond 2 fingers nor effaced. Extraperitoneal section was chosen because of prolonged labor and ruptured membranes, temperature of 102.4° F. and very foul vaginal discharge. The fetal heart was questionably present before operation, but the baby was dead when extracted. The mother had a foul wound infection at the drain site, and was not discharged until completely well and healed on the twenty-third postoperative day.

The operating time is of interest, recalling the objection that extraperitoneal operations are long, time-consuming operations, and conducive to surgical shock. In the author's personal group, the operating time ranged from 29 to 60 minutes. Excluding the first two cases, each one hour long, the average operating time for 17 cases was 38.5 minutes. The operating time for the entire group ranged from 29 to 82 minutes, averaging 54 minutes.

The average stay in the hospital was 18 days, although half of the patients were discharged within 14 days. One case each of bronchopneumonia, pulmonary infarct and thrombophlebitis, and antepartum and puerperal psychosis with stays of 23, 52, and 23 days affected the average stay. All patients were kept until healed and ambulatory.

Exact data were available on hours of labor and ruptured membranes in 30 cases. The average hours of ruptured membranes was 38½, two-thirds of the group had ruptured membranes more than 24 hours. Labor had been present for an average of 53 hours. All but one had labored more than 24 hours, and 21 had pains more than 48 hours. Fourteen cases had fever preoperatively. Twenty-six cases had postoperative morbidity, although in 20 cases the temperature was normal after the third day even though in a few instances the drainage was purulent.

Operative Accidents.—In earlier experience the peritoneal cavity was opened six times before the uterus was incised, and immediately repaired. In one instance the peritoneum was noted as lacerated after extraction of a 9.25 pound baby.

Six babies weighed over 9 pounds, one over 10. One had a tremendous hydrocephalic head which well tested the operative field and uterine incision capacity. The patient had a 35-minute operation, without peritoneal laceration, after 48 hours of labor. There was a slight temperature for 6 days, and the patient was discharged in 14 days. The indication for abdominal delivery over delayed craniotomy was on religious grounds of the patient's election.

As noted in the table, cephalopelvic disproportion accounted for 27 of the operations. Of the 3 patients previously sectioned, 2 were not seen until labor with ruptured membranes had progressed for many hours beyond the "12-hour safe period." One, in spite of clinic talks and warnings, came in with a history of ten days' ruptured membranes. The third had defect in the old scar the size of a dime. The defect, obviously long existing, was clean and bloodless. Forty-eight hours of labor had not extended the defect in the lower segment of the uterus, although the membranes had ruptured through it, distending the retrovesical area with amniotic fluid!

Six patients had wound infections in and about the site of drainage, and 2 wounds were grossly infected although all eventually healed well. The remainder healed promptly after removing the supravesical drain.

SUMMARY

In presenting this technique, recognition is extended to previous observers and operators who attempted the same or similar approaches to the lower uterine segment. From Physick in 1824 to Furness in 1930, this approach has repeatedly seemed the most rational and direct. The difficulty largely seems to have been in not using incisions through the perivesical fascia, not freeing the bladder adequately from the uterus, not distending and emptying the bladder in the early stage of the operation, not fully utilizing the lower segment of the uterus for the incision, and not using an incision designed to facilitate the extraction of a large size baby's head.

The various transperitoneal operations developed in the search for satisfactory true extraperitoneal operations are effectual for the usual case. But one cannot expect consistently good results in presumably or actually infected cases. It is in this group that the true extraperitoneal operation affords the greatest protection to the patient and solace to the obstetric surgeon.

Of the various extraperitoneal operations, Jellinghaus' revival of interest in the Latzko technique has made it one frequently used.

The Latzko technique embodies certain features and hazards which sharply curtail its use and confine its appeal. The lateral displacement of the bladder carries the operation into an easily infected zone of restricted space, and compromises the safety of important structures.

The direct supravesical approach is by every criterion the logical one, and when combined with procedures designed to eliminate the objections to other techniques, gives an extraperitoneal operation of an ideal type.

The operation described in this paper seems to fulfill such requirements. It is truly extraperitoneal, and meets all demands for safety. Of outstanding importance is the fact that the technique is attained by operators of average ability, and it has been successfully performed by obstetric residents without special surgical training. In the entire series reported, there were no serious accidents and no maternal deaths. The accident of peritoneal puncture has been eradicated by familiarity with the technique.

It is our belief and hope that further experience in other hands will demonstrate the factors of technical facility, safety, celerity, and satisfactory results which we believe it commands.

NOTE: When this manuscript was submitted for publication, more than 60 operations of the type described had been successfully performed with two fetal and no maternal deaths. These were largely done on "bad risk" cases.

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DISCUSSION

DR. HENRY T. BURNS.—Before I wrote my first paper on the Latzko operation, I reviewed the literature and neither in German nor American writings was there any detailed description of how the Latzko cesarean section should be performed. All we could find was that the bladder should be displaced to the right, the peritoneal reflection upward, exposing the lower uterine segment by a longitudinal incision.

I have had difficulty in only three of the 58 Latzko operations I have performed. This occurred when the drain was removed before the drainage tract was well established. By passing a sound, opening up the tract and thus obtaining free

drainage I have always succeeded in obtaining prompt healing of the wound and subsidence of temperature. I have never seen the ureters, though I make it a practice of looking for them. There were no maternal deaths in my 58 cases.

From the way Dr. Waters has described this technique and from the results he has obtained, I am inclined to think that this procedure carries with it much less danger than the Latzko extraperitoneal cesarean section. We should have some one in every community who can do a true extraperitoneal cesarean section of some type on frankly infected patients. In this way we can obtain a living baby instead of sacrificing the baby or the uterus through a Porro cesarean section.

DR. HARBECK HALSTED.—I see no reason why this operation should take the place of the Latzko operation in the frankly infected case. It is more difficult to do, it has no great advantages, and I think the results will prove no better.

Formerly I believed that the extraperitoneal operation should be used in all cases. I first did one on a patient who was in labor about four hours with very great ease. I then tried it on two patients who had not been in labor at all. In the first instance it was done extremely easily, but in the second case the dissection between the bladder and the uterus was very difficult, but it was eventually accomplished.

I feel with Dr. Burns that the extraperitoneal operation is an extremely valuable operation, that it is not done often enough, and I would like to see it developed, so that it can be used on patients who have not been in labor.

DR. ALFRED C. BECK.—From a long experience with the transperitoneal low cesarean section, I am satisfied that many of the neglected cases should be handled by the transperitoneal route.

This procedure does not appear to be very difficult and, because not only peritoneum but fascia and bladder separate the uterine wound from the peritoneal cavity, it should give greater protection than any of the other cesarean techniques.

The original extraperitoneal procedure was recommended by Physick who was an anatomist and not a surgeon. He recommended it to Dewee, who referred to it in a footnote in one of the early editions of his textbook. Dewee apparently did not do the operation and omitted it from subsequent editions of his book.

Early in this century, Frank and Selheim actually tried the operation as suggested by Physick. They attempted to separate the peritoneum from the paravesical fascia and enter the uterus through the space thus prepared. Because of their inability to dissect off the peritoneum, Kroenig devised his transperitoneal low section which he thought would accomplish the same purpose, since the uterine wound was covered by peritoneum and the bladder. The operation of Dr. Waters is a distinct improvement and merits a trial.

DR. ALBERT ALDRIDGE.—At the Woman's Hospital, we have adopted the extraperitoneal cesarean section for selected cases and have done about 40 such operations with only one death. This was due to late embolism at a time when the patient was free of postoperative fever.

Some time ago, I reported before this Society, on the results of a series of cases that had been operated upon at the Woman's Hospital and suggested some modifications in the Latzko technique. These modifications included a procedure to provide more room for the delivery of the child. We found that under the most favorable conditions the space that could be had by careful dissection was frequently so small that there was great risk of injury to the bladder or uterovesical fold during extraction of the child.

I had considered a modification in the technique exactly like the one which Dr. Waters has presented and had tried to carry out the same procedure by blunt dissection. The uterovesical fold is usually so adherent to the fundus of the bladder, that I am convinced these structures cannot be separated except by sharp dissection. If experience proves that we can routinely carry out the dissection as described by Dr. Waters, without too much danger of injury to the bladder or uterovesical fold of peritoneum, I feel that he has added an important step in the technique of extraperitoneal cesarean section. This seems the most logical approach to the lower uterine segment.

In doing cesarean section at the Woman's Hospital, we almost invariably use a transverse incision in the lower uterine segment.

DR. WATERS (closing).—In answer to Dr. Halsted who regards the operation as dangerous, I would say that the first five minutes may be said to be meticulous, very slightly dangerous, but not difficult. The rest of the operation is as simple as any low laparotrachelotomy. The entire procedure depends upon getting the peritoneum, with its perivesical fascia attached, off the fundus of the bladder. There is plenty of room, for I delivered one baby with a tremendous hydrocephalic head. I defy any Latzko approach, even with the excellent addition of deliberately incising the peritoneal fold, to provide room for that particular head.

After the first case, in which the operation was deliberately planned and done, I looked for suitable cases in order to develop the technique; not finding them fast enough, I did this operation on several cases where elective procedures were to be done. It was just as easy as those of the other type.

I put in a self-retaining catheter, because with that much manipulation in the pelvis it is wise to give the bladder a rest for forty-eight hours. The catheter keeps the bladder collapsed.

THECA CELL TUMORS OF THE OVARY*

A Report of Ten Cases

Malcolm B. Dockerty, M.D., Rochester, Minn.
(From the Section on Surgical Pathology, The Mayo Clinic)

In 1932 Löffler and Priesel[1] described six "xanthic" tumors of the ovary which they considered as arising from the cells of the theca interna. In 1934 these same authors added four similar cases. Their reports were followed by those of Melnick and Kanter,[2] Kellert,[3] Geist and Speilman[4] and others. In 1938 Geist and Gaines[5] added a comparatively large series of 5 cases and brought to 22 the number of recorded theca cell tumors. The gynecologic literature now contains about 25 examples of this rare neoplasm.

HISTOGENESIS

Much controversy has arisen not only as to the histogenesis but also the actual nature of these tumors. Löffler and Priesel early recognized the close resemblance between the cells of the tumor and the cells of the theca interna itself. However, most of the tumors they reported were large, so that an actual point of origin could not be definitely established. Others disagreed and at present there are three theories to explain the origin of theca cell tumors. Proponents of the first theory believe these neoplasms are derived from the ovarian stroma and regard them as luteinized fibromas. A second group holds that the tumors are luteinized granulosa cell tumors and that they should not be called "theca cell tumors." Finally, many prominent gynecologists believe with Löffler and Priesel that the tumors arise from theca cells and represent a separate entity. Experimental evidence would tend to support this third view.[6]

*Submitted for publication, September 8, 1939.

CLINICAL FEATURES

The clinical features usually associated with theca cell tumors resemble closely those found in association with granulosa cell tumors of the ovary. More than 80 per cent of the neoplasms occur after the menopause and produce vaginal bleeding which may or may not be periodic. Those tumors reported among patients of the younger age groups have usually been associated with amenorrhea or with menometrorrhagia. The clinical picture is usually not so uniform as it is in the presence of a granulosa cell tumor, and some theca cell tumors apparently produce no menstrual abnormalities. As with granulosa cell neoplasms, the symptoms are caused by the secretion of estrin by the cells of the ovarian neoplasm as demonstrated by assay of tumorous tissue.

PATHOLOGIC FEATURES

Despite arguments to the contrary, there seem to be certain gross and microscopic features peculiar to all neoplasms of this so-called theca cell group. The tumors are fibrous, solid, usually encapsulated and are canary yellow in color. On section the "liver sausage" consistency of granulosa cell tumors is lacking and, except for the yellow color, a diagnosis of fibroma would seem justified on the basis of gross inspection. A thin "rind" of ovarian tissue can usually be shelled from the surface of the tumor in the form of a smooth "capsule."

Histologically, the cardinal features are the predominance of plump fusiform cells with vacuolated cytoplasm and oval nuclei. An epithelioid appearance is sometimes assumed. Intracellular fibrils are often abundant, in contradistinction to the picture seen in specimens of granulosa cell neoplasm. The tumor cells and the interstitial substance both tend to undergo extensive hyalinization—a process which often occurs in irregular bands. Stains for lipoid reveal the presence of fatty droplets within the cytoplasm of the tumor cells and, to a lesser extent, in the intercellular substance. These fatty deposits tend to be more concentrated about the periphery of the zones of hyalinization. The distribution of lipoid differs from that observed in luteinized granulosa cell neoplasm, in that it is intracellular. Chemically, also, a difference exists.

MATERIAL AND METHODS

A review of the pathologic material examined at the Mayo Clinic revealed 10 ovarian neoplasms with gross and microscopic features which warranted a revised diagnosis of theca cell tumor. Multiple sections were recut from these tumors and stained routinely with hematoxylin and eosin. In addition, stains for lipoid were made in every instance as confirmatory diagnostic evidence. The pathologic and clinical features of these ten cases as herein reviewed, are submitted not with the idea of settling controversial issues concerning histogenesis, but with the purpose of adding to the literature examples of a tumor which, until recently, has received little attention in gynecologic writings.

CASE 1.—A white multipara, 56 years old, came to the Mayo Clinic on May 23, 1938, complaining of postmenopausal bleeding. Her family history and personal history were irrelevant. Menstrual history had been normal, her three pregnancies uncomplicated, and her menopause at the age of 50 was without unusual incident. Four years prior to admission her present illness had begun with a resumption of "menstruation." These episodes of bleeding occurred with approximately cyclical regularity every two or three weeks, usually lasted three to five days, and were frequently accompanied by the passage of large clots of blood. A slight purulent "intermenstrual" discharge had been noticed for six months.

Examination disclosed an enlarged uterus with a palpable right ovarian mass which was slightly tender. Results of laboratory examinations were essentially negative.

At operation on May 28, 1938, subtotal hysterectomy was done with removal of the adnexa because of uterine fibroids and a solid tumor which involved the right ovary. The patient was dismissed twenty-three days later, following a normal convalescence.

Fig. 1.—(Case 1.) Posterior view of a theca cell tumor of the right ovary, with an enlarged uterus which contains fibromyomas.

The operative specimen consisted of the uterus, both Fallopian tubes and both ovaries. The uterus was large and contained multiple small fibromyomas. Both tubes and the left ovary were normal on gross inspection. The right ovary was enlarged and on section presented a brownish yellow, solid, tumor nodule, 3 cm. in diameter (Fig. 1).

Histologic sections of interest were limited to the endometrium and the right ovarian tumor. The latter was seen to consist of plump spindle cells with central nuclei and relatively prominent nucleoli. The nuclei were oval, dark-staining and showed on an average, three mitotic figures per thousand cells. The cytoplasm was relatively clear, finely granular, and occasionally vacuolated (Fig. 2, *a*). Fibrous tissue was not abundant and tended to be arranged in bands which showed partial hyalinization. Around these portions the tumor cells appeared in palisade formation. Stains for lipoid revealed the presence of fat in the tumor cells, especially in relation to the zones of hyalinization (Fig. 2, *b*). The remnant of normal ovary which lay stretched out over the surface of the tumor showed an entire lack of maturing follicles and corpora lutea. The endometrium was polypoid and reflected in most sections the action of estrin. Here and there, however, were

regions wherein the glandular tubules were slightly coiled so as to suggest an early secretory or differentiative phase. Cysts were fairly numerous and suggested a lack of the hormone of the corpus luteum.

CASE 2.—A white multipara, 53 years old, entered the clinic May 8, 1929, complaining of postmenopausal bleeding. The patient's history was irrelevant. Her menstrual periods had been scanty and irregular for two years, and one year prior to admission they had ceased for a period of six months. Six months prior to admission the "menses" had returned, somewhat irregular in time and duration.

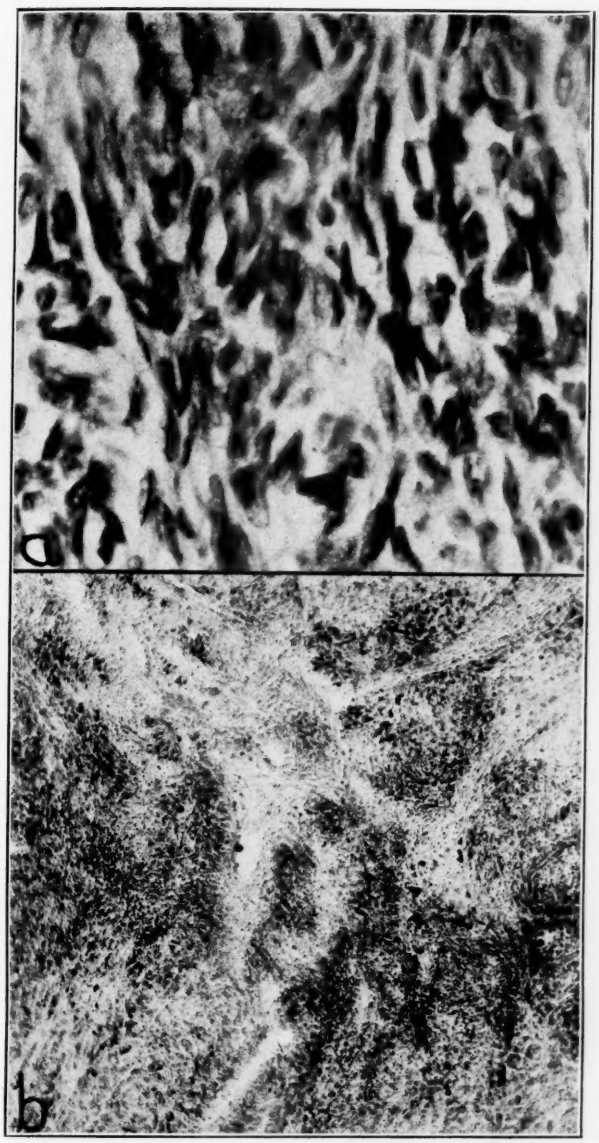

Fig. 2.—*a* (Case 1), Section of a theca cell tumor of the ovary, the cells of the tumor presenting a spindlelike appearance, but the granulosa cells being, in contrast, round (hematoxylin and eosin; ×600); *b*, section of a theca cell tumor (same case as Fig. 2,*a*) showing deposits of lipoid concentrated around zones of hyalinization (sudan III; ×100).

The essential, positive observations on examination were uterine fibromyomas and mild hypertension.

At operation on May 10, 1929, hysterectomy with bilateral salpingo-oophorectomy and appendectomy were performed because of uterine fibromyomas and a solid left ovarian tumor. The patient was discharged on the nineteenth day postoperatively. Six years later she reported herself as being in excellent health.

The pathologic findings were almost identical to those described for Case 1 and will not be detailed. The theca cell tumor measured 2 cm. in diameter and involved the left ovary (Fig. 3, *a*). The uterus was enlarged (195 gm.) and contained small

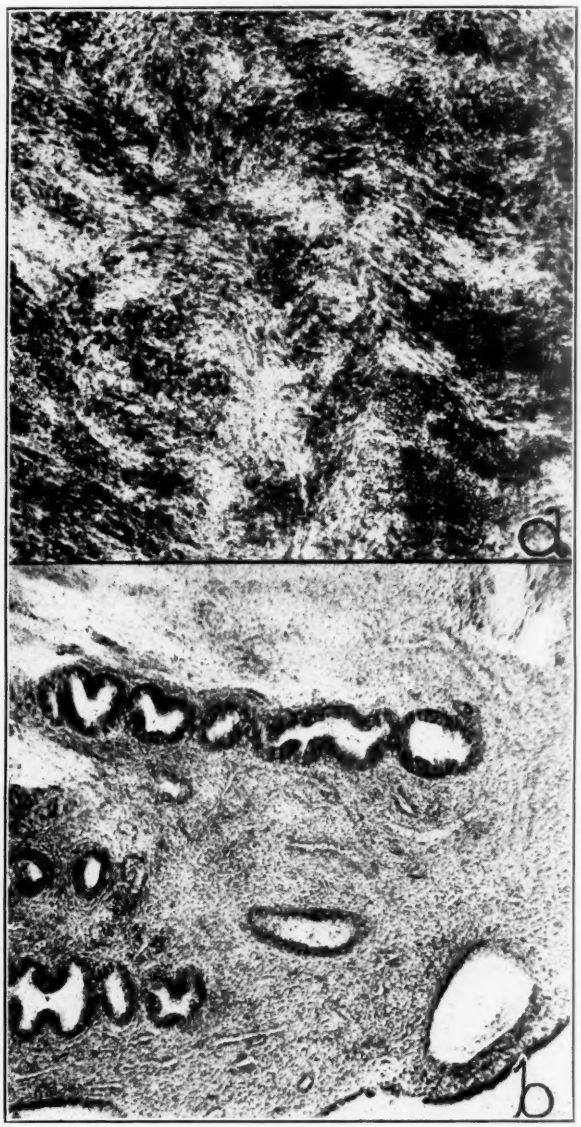

Fig. 3.—*a* (Case 2), Theca cell tumor of the left ovary, with a large amount of intracellular lipoid. Some hyalinization is present in bandlike regions (sudan III; ×100); *b* (Case 2), region in endometrium showing coiling of tubules; a "progesterone" effect is suggested (hematoxylin and eosin; ×10).

fibroids. The endometrium was cystic and reflected the action of estrin, but certain regions contained coiled glands suggesting the influence of progesterone (Fig. 3, *b*).

CASE 3.—A white multipara, 56 years old, entered the clinic on Jan. 17, 1914, complaining of persistence of her menstrual periods. For seven years menses had been prolonged, with heavy flow. For one year she had menstruated almost daily.

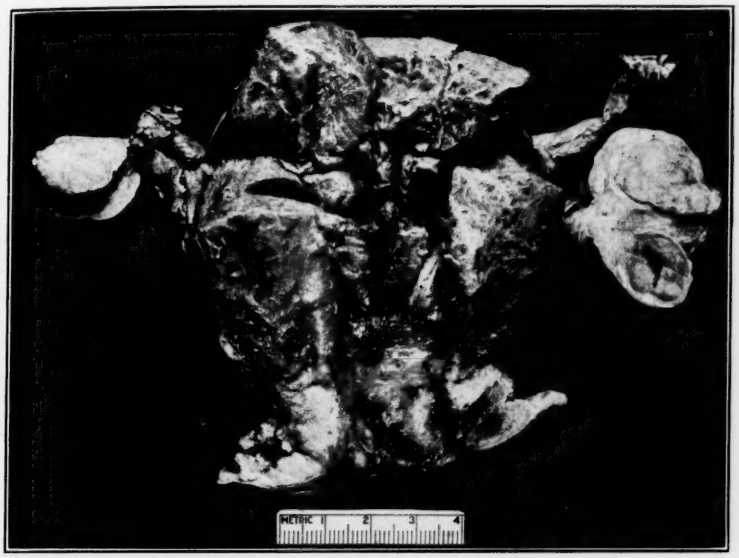

Fig. 4.—(Case 3.) Theca cell tumor of the left ovary, showing grossly an extreme degree of uterine myohyperplasia and thick endometrium.

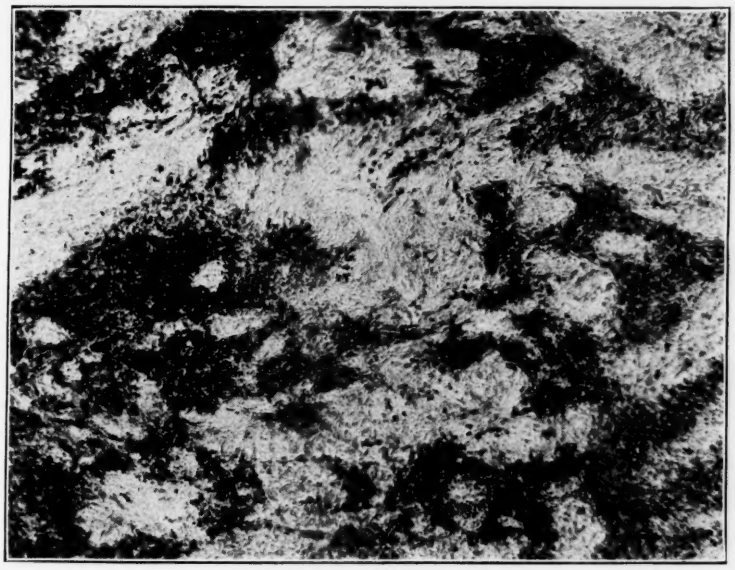

Fig. 5.—(Case 3.) Typical microscopic picture of a theca cell tumor with extensive hyalinization. The dark-staining areas represent lipoid accumulation (sudan III; ×100).

Examination disclosed an enlarged, boggy type of uterus and a mass in the region of the left adnexa.

At operation on Jan. 20, 1914, hysterectomy with bilateral salpingo-oophorectomy was done because of a solid tumor of the left ovary. The patient was discharged on her fourteenth day postoperatively. Efforts to follow this patient proved unsuccessful. Grossly, the uterus was considerably enlarged, measuring 6 by 5 by 4 cm. (Fig. 4). The endometrium was thickened. Both Fallopian tubes presented chronic inflammatory changes. The right ovary was atrophic. In the left ovary was a yellowish, solid, encapsulated tumor nodule 3 cm. in diameter. Histologically, this tumor was seen to be composed of plump spindle cells loaded with lipoid. Hyalinization was seen in bandlike portions in many sections (Fig. 5). Mitoses were scanty. The endometrium was of the glandular cystic type, with little evidence of activity of the hormone of the corpus luteum.

CASE 4.—A white multipara, 55 years old, entered the clinic on Oct. 4, 1924, because of a continuous blood-tinged vaginal discharge two years in duration. Ten years previously she had passed through an apparently normal menopause.

Pertinent observations were limited to the pelvis, where a tumor was palpated in the left adnexal region.

At operation on Oct. 10, 1924, hysterectomy with bilateral salpingo-oophorectomy was performed because of a solid tumor, 6 cm. in diameter, involving the left ovary. The patient was well when she was last heard from on Dec. 6, 1931. Pathologic observations were a slight enlargement of the uterus, which structure contained cystic endometrium. The condition of both Fallopian tubes and the right ovary was not remarkable. The left ovarian tumor measured 10 cm. in diameter, was solid in consistency, and yellow in color. Histologically, it presented all the typical features of a theca cell tumor. Hyalinization was a prominent feature.

CASE 5.—A white primipara, 26 years old, entered the clinic on May 15, 1911, with the complaint of easy fatigability. Menses had begun at the age of 18 years and had always been irregular and scanty. For the preceding year mild vaginal bleeding had been a daily occurrence.

Pertinent observations on examination were a symmetrically enlarged thyroid gland, compensated mitral heart disease, an enlarged uterus, and a nodular pelvic tumor.

At laparotomy on May 24, 1911, a yellowish fibroid tumor involving the left ovary was removed and appendectomy was performed. The patient was dismissed from the hospital on the eleventh day postoperatively. She was living and well when last heard from in 1931.

The ovarian tumor measured 5 cm. in diameter, was yellow in color, and fibrous in consistency. Histologically, it proved to be a theca cell tumor with extensive deposits of lipoid.

CASE 6.—A white primipara, 48 years old, entered the clinic on Jan. 3, 1910, complaining of a pelvic tumor. Her history was irrelevant to her condition at entrance. Her last menstrual period had occurred one year previously. Two years prior to admission a pelvic tumor had been discovered in the course of a medical examination for "irritable bladder."

Examination disclosed a large, firm, freely movable mass in the posterior portion of the cul-de-sac of Douglas.

At operation on March 30, 1910, subtotal abdominal hysterectomy was done, with removal of the adnexa because of a solid tumor of the right ovary. The peritoneal cavity contained a small amount of free fluid. The patient reported "no recurrence of trouble" in 1915.

The right ovarian tumor was solid and measured 4 cm. in diameter. Histologically it presented the characteristics of a theca cell tumor, but contained only a moderate amount of lipoid substance. The endometrium was cystic and rather atrophic.

CASE 7.—A white multipara, 58 years old, entered the clinic on July 13, 1934, complaining of postmenopausal bleeding. Her history was irrelevant to her condition at entrance. Menses had always been regular and her menopause at the

age of 48 had had no unusual features. Her present illness had begun one year prior to admission and took the form of two episodes of vaginal bleeding associated with lower abdominal cramping pain of menstrual type. A tumor of the left ovary had been discovered on routine physical examination four years previously.

Examination disclosed a tumor in the left side of the pelvis. The possibility of this tumor's being a granulosa cell neoplasm was considered. Operation was advised but was deferred by the patient.

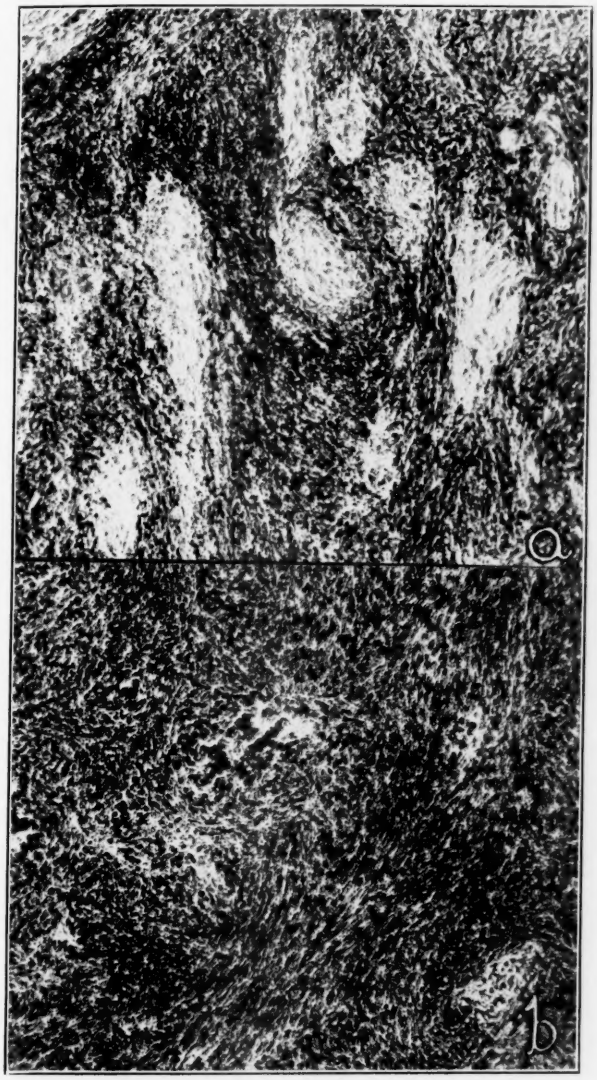

Fig. 6.—*a* (Case 7), Section of a typical theca cell tumor, with bandlike regions of hyalinization (sudan III; ×100); *b* (Case 7), another region of the same tumor; some of the cells are definitely of the granulosa type (hematoxylin and eosin; ×100).

She returned two years later because the abdominal tumor seemed to be increasing in size. Examination confirmed this suspicion and on April 14, 1936, exploration was carried out. Left salpingo-oophorectomy was done because of a large solid tumor which involved the left ovary. Postoperative convalescence was normal and the patient was dismissed after nineteen days of hospitalization.

The ovarian tumor was solid, yellowish, and measured 15 cm. in its greatest diameter. It could best be described as a "yellow fibroma." Histologically most portions of the tumor were typical of theca cell tumor with rather extensive hyalinization. In other portions, however, the picture was that of a granulosa cell tumor of the cylindroid type (Fig. 6, *a* and *b*).

CASE 8.—A white multipara, 58 years old, came to the clinic on July 9, 1931, complaining of vaginal bleeding of one month in duration. The bleeding had begun as a frank flow of bright red blood and had continued as a blood-tinged discharge. The patient's history otherwise was irrelevant to her condition.

Essential observations on examination were an adenomatous goiter and an enlarged uterus.

On July 11, 1931, dilatation and curettage revealed a carcinoma of the fundus uteri. Abdominal hysterectomy was thereupon carried out, with removal of both adnexa. On several subsequent visits there was no evidence of recurrence of malignancy. In January, 1939, the patient reported that she was well.

Pathologic features of interest were the large uterus, which weighed 200 gm. and which was the seat of a Grade 2 (on the basis of 1 to 4) adenocarcinoma measuring 3 by 3 by 2 cm. The condition of both Fallopian tubes and the right ovary was not remarkable. The left ovary was the seat of a solid neoplasm 4 cm. in diameter, which was smooth on surface and yellowish on section. Histologically, this proved to be a typical theca cell neoplasm.

Cases 9 and 10 presented incidental observations—one (Case 9) an accidental finding of a theca cell tumor 1 cm. in diameter afflicting an elderly patient dying of bronchopneumonia, and the other (Case 10) a theca cell tumor 2 mm. in diameter discovered in a patient undergoing hysterectomy for fibroid tumor. In neither instance were there any clinical symptoms suggestive of ovarian pathologic processes.

COMMENT

In the present study all the specimens were preserved in formalin, a circumstance which precluded hormonal studies. However, certain data are at least suggestive of a hormonal effect. Of 8 uteri available for examination, 7 were considerably enlarged and 3 contained fibroid tumors. The endometrium, also, in 6 of these 8 cases, was of the glandular cystic type, reflecting the prolonged action of estrin, probably unopposed by the action of progesterone. In two instances the endometrium presented evidence of glandular coiling indicative of differentiation and suggestive of a progesterone effect.

The one example (Case 8) of an associated endometrial carcinoma is interesting. In a series of 32 cases of granulosa cell neoplasms, we have seen 3 cases with associated carcinoma of the endometrium and other investigators have reported a similar finding. This incidence of 10 per cent seems more than coincidental and raises the question of the carcinogenetic properties of estrin.

All the neoplasms fulfilled the gross diagnostic criteria laid down for theca cell tumors and 8 of the lesions were typical histologically. In 2 instances histologic features typical of granulosa cell neoplasm were present in scattered regions throughout the tumor. This observation is not new, having been previously reported by Greenhill and Greenblatt.[7]

Nine of the 10 patients were more than 45 years of age. This is in keeping with the observations of others that theca cell tumors occur most frequently after the menopause. It has been generally conceded that theca cell tumors are, at most, of a low grade of malignancy.

The present series does not argue much for or against this point. All that can be said is that, on the basis of traced patients, the prognosis following removal of theca cell tumors is much better than it is for solid carcinomas of the ovary.

SUMMARY

The clinical and pathologic data on 10 so-called theca cell tumors have been presented. These tumors occur most frequently following the menopause. They resemble granulosa cell tumors clinically, but pathologically possess certain distinguishing features which probably justify their consideration as an entity.

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HEART DISEASE AND PREGNANCY

An Eight Years' Experience

Julius Jensen, M.D., Carl Wegner, M.D., Edgar H. Keys, Jr., M.D., and Hugh R. Smith, M.D., St. Louis, Mo.

(From the Departments of Obstetrics and Medicine, Washington University)

INTRODUCTION

ON NOV. 1, 1930, the Medical Consulting Service of the Prenatal Clinic in the Department of Obstetrics of Washington University was reorganized. One afternoon a week a member of the Obstetrical Staff (C. W.) and one internist (J. J.) examine together all obstetric patients who present medical problems, a great many of which are referable to the cardiovascular system. Those found to be suffering from organic heart disease receive special records which are kept in a separate file. From Nov. 1, 1930, to Dec. 31, 1938, the clinic has followed 108 such patients. Five additional patients were included in this study, because they presented points of special interest; they were all seen in St. Louis Maternity Hospital. The subsequent analysis is made to determine to what extent the care extended to this class of patient has affected maternal and infant death rates.

ANALYSIS OF MATERIAL

Incidence.—The experience of Washington University Obstetrical Department regarding incidence of heart disease conforms quite well to the general experience on these points. During the period of observation 8,843 patients were registered in the Clinic. One hundred and twelve, or 1.27 per cent, of these were found to have heart disease.

Race.—Ninety-three (or 79.5 per cent) of the patients were white, and 24 were negroes.

Age.—One hundred eight surviving patients were distributed according to age (Table I). In the following column these figures were transposed into percentage distribution. In the last column is given for control a similar distribution found by Jensen (p. 157).

Gravidity.—One hundred eight surviving patients were similarly distributed according to parity (Table II).

TABLE I

AGE GROUP	NO.	PERCENTAGE DISTRIBUTION	CONTROL
19	18	17	4
20–24	33	30	24
25–29	28	26	29
30–34	15	14	23
35–39	9	8	14
40–	5	5	6
Total	108	100	100

TABLE II

PARITY	NO.	PERCENTAGE DISTRIBUTION	CONTROL*
0	44	41	38
1	31	29	20
2-4	24	22	28
5 plus	9	8	14
Total	108	100	100

*Jensen, J.: The Heart in Pregnancy, St. Louis, 1938, The C. V. Mosby Co., p. 194.

TABLE III

Rheumatic heart disease	99
Congenital heart disease	7
Syphilitic heart disease	2
	108

Etiology.—Etiologically the patients were distributed as shown in Table III.

Thus, 89 per cent of these patients had rheumatic heart disease. That 7 patients had congenital heart disease is almost three times as many as expected (Jensen, p. 296). We were very critical in the diagnosis of congenital heart disease and are well aware that functional murmurs may closely mimic congenital heart disease. Nevertheless, we believe the diagnosis is beyond doubt in these 7 cases, though we failed to diagnose the exact lesion in 3. In 3 others, patent ductus arteriosus and in one Roger's disease was thought to be the dominant lesion. None of the patients were markedly cyanotic. Both of the patients with syphilitic heart disease had aortic regurgitation and positive serologic tests for syphilis.

Patients who had hypertension or other evidence of degenerative heart disease and who did not at the same time suffer from any other form of organic heart disease were not included in the series. Reference to two patients with kyphoscoliotic heart disease has previously been published (Jensen, p. 337).

Anatomic Lesion.—Ninety-nine surviving patients with rheumatic heart disease presented valvular lesions as shown in Table IV.

Six foot films of the chest were taken of 64 patients. In 13 cases the cardiac shadow was within normal size, but in only 7 also of normal shape. In 42 cases the left border showed the convexity characteristic of mitral disease. Twenty-two cardiac shadows were enlarged 1 degree, 14 were enlarged 2 degrees, and 6 were enlarged 3 degrees.

TABLE IV

	NO.	PERCENTAGE DISTRIBUTION	CONTROL JENSEN (P. 170)
"Mitral"	3	3	--
Mitral regurgitation	11	11	40
Mitral stenosis	35	35	20
Mitral stenosis and regurgitation	39	40	29
Aortic lesions	4	4	4
Aortic and mitral	7	7	5
Total	99	100	98

TABLE V

CLASS	NO.	PERCENTAGE DISTRIBUTION	CONTROL (JENSEN P. 41)
I	46	39	36
II, a	44	37	32
II, b	25	21	24
III	4	3	8
	119	100	100

Cardiac Function.—Arrangement according to the functional classification of the American Heart Association is shown in Table V. All cases were here included.

Twenty-seven (or 22.7 per cent of all the cases) patients showed, some time during the pregnancy, signs of congestive failure (i.e., râles, edema, dyspnea, and tachycardia).

An attempt was made to correlate the size of the heart on the x-ray film with functional classification, but this was not feasible, possibly because the number of cases was too small.

Acute Rheumatic Carditis.—One patient had acute rheumatic carditis with symptoms so marked that the pregnancy was interrupted and the patient sterilized. The patient was followed for over four months, her course was unsatisfactory though she did not develop severe congestive failure.

Toxemia of Pregnancy.—Four patients with increased blood pressure were observed; in none of them did the condition progress so far as to cause serious trouble. There was no evidence that patients with rheumatic heart disease are especially liable to eclampsia. Nephritis was not diagnosed in this series.

There was nothing to show that these patients as a group did worse than a similar group of nonpregnant cardiac patients might have been expected to do.

Abnormalities of Impulse Formation and Conduction.—Paroxysmal tachycardia was diagnosed 3 times in this series. In none of them did the pregnancy seem to affect the tendency to the attacks.

Auricular fibrillation was found in two patients with rheumatic heart disease, both of whom died. One was the fatal Case 1 which was first seen near term, and the other was the fatal Case 6. This patient developed the arrhythmia in the final stages of her illness, at first in attacks and, later, permanently. Thus we can confirm the impression (Jensen p. 179) that auricular fibrillation is rare in pregnant women with rheumatic heart disease and that it is a sign of grave prognosis.

Bundle branch block was present in our fatal Case 1 and also in a 34-year-old gravida iv who had undergone thyroidectomy fourteen years before. In 1931 and in 1933 she had been delivered in St. Louis Maternity Hospital. Immediately following delivery she developed pulmonary edema and became dyspneic and cyanotic. She improved promptly under treatment and was discharged in good health. She has remained well since. Following this episode careful examination revealed signs of mitral stenosis, and x-ray examination showed marked enlargement of the heart shadow. The electrocardiogram showed bundle branch block.

However, our experience may not reflect the true incidence of the defect, for because of the relatively small value of the electrocardiogram in this problem, only 27 of our cardiac patients were electrocardiographed.

Interruption of Pregnancy.—Thirteen, or 11.4 per cent, of all pregnancies observed ended with the death of the baby. One patient had a spontaneous miscarriage, two babies died undelivered, and three pregnancies were interrupted before the child was viable. Three were stillborn and 4 died post partum. However, if only those cases were considered in which the pregnancy was carried beyond thirty-six weeks, the death rate was only 4, or 3.79 per cent.

Artificial interruption of pregnancy was performed only twice, and we do not believe that so conservative a management did any substantial harm to the mothers. Thus our experience confirms the view prevailing in the literature that premature interruption of pregnancy should be restricted to those cases where congestive failure fails to respond to the best available treatment.

Maternal Deaths.—During the period under consideration, 8 women died in St. Louis Maternity Hospital with heart disease. Their cases are here briefly abstracted.

CASE 1.—(No. 13450.) Primigravida, aged 40 years. History of rheumatism in childhood. Rheumatic, mitral heart disease. Blood pressure: 190/140. Admitted when thirty-two weeks pregnant with congestive failure which progressed in spite of medical treatment. After nine days in hospital, Cesarean section. Child lived. Anesthesia: pantopone, hyoscine, local. Two hours after operation collapse and death. No autopsy.

CASE 2.—(No. 14106.) Colored primigravida, aged 18 years. When four months pregnant, she developed dyspnea. Pneumonia and colds during next three months. When seven months pregnant she appeared at St. Louis Maternity Hospital. As she was not very sick she was told to return next day. She arrived by street car at 2 P.M. She had dyspnea which rapidly increased, and she developed pulmonary edema from which she died at 9 P.M. Post-mortem examination: button hole mitral stenosis. Heart's weight 235 Gm. Pulmonary edema.

CASE 3.—(No. 14677.) Tertigravida. Two previous miscarriages. Double mitral lesion. When twenty-eight weeks pregnant, she developed an upper respiratory infection. Against instructions she stayed away from the Clinic. Near term she was admitted to the St. Louis Maternity Hospital in labor. When the os was fully dilated she suddenly became cyanotic and dyspneic. She was rapidly delivered of a living infant. Following this she continued to improve for about twenty-four hours when she relapsed and died with pulmonary edema, about thirty-eight hours post partum. Post-mortem examination: the heart weighed 865 Gm. Marked mitral stenosis. Pulmonary edema. Congestion of liver. No peripheral edema.

CASE 4.—(No. 15943.) Quadrigravida, aged 26 years. Mitral stenosis. Rheumatic fever aged 7. Decompensated (?) during last two pregnancies at six and eight weeks, respectively. Entered Maternity Hospital on Jan. 4, 1933, twelve weeks pregnant, because of cardiac symptoms. On Jan. 14, 1933, hysterectomy. Morphine, hyoscine, local anesthesia. Four days postoperatively she developed right lower lobar pneumonia. Sixteen days postoperatively collapse and death. No autopsy.

CASE 5.—(No. 20699.) This case of subacute bacterial endocarditis has been reported in detail by Jensen (p. 288).

CASE 6.—(No. 21531.) Decigravida, aged 38 years. Eight pregnancies ended in miscarriages, 6 of which were induced. One living child was born at seven months. Chorea at 14, rheumatic fever at 16 years of age. First seen at the St. Louis County Hospital, when four months pregnant, with mitral stenosis and regular rhythm. Early decompensation. She was admitted to St. Louis Maternity Hospital and responded well to treatment. During the next two or three months, she was followed as an out-patient at the County Hospital. At seven months, when hardly compensated she was delivered of a seven months' baby which died soon

after birth. About this time she developed auricular fibrillation. She was discharged apparently compensated. She was found dead in bed twenty days post partum. No post-mortem examination.

CASE 7.—(No. 30376.) Secundigravida, aged 32 years. Five years ago "leakage of the heart" was diagnosed. During this pregnancy, dyspnea was present, and near term she had some edema of the ankles. Near term she caught a cold. During labor she received no inhalation anesthesia. Following delivery the cold became worse and in four or five days, she developed pneumonia. Nineteen days postpartum the temperature became normal, but one week later she again developed fever associated with findings in her lungs. Diagnosis of mitral stenosis was confirmed. She died thirty-six days post partum. The child lived. No post-mortem examination.

CASE 8.—(No. 31862.) Primigravida, aged 28 years. Seen in St. Louis City Hospital, when twelve weeks pregnant, with pneumonia, syphilis, and disease of the mitral and aortic valves. At age of 18 she had had a rheumatic (?) infection. Her heart disease was considered rheumatic in nature. When thirty-eight weeks pregnant, she became decompensated, and was admitted to the hospital. At term she was delivered of a live child, but following this she continued in congestive failure which did not respond to treatment. She died at home, 7 weeks post partum.

Among the 7 patients whom we know to have died from congestive heart failure, 2 had been classified as Group 3, 3 as Class 2b, 1 as Class 2a, and 1 as Class 1. Both of these last two, however, had a third degree enlargement of the x-ray shadow of the heart. This classification was found to be a valuable, though not absolute, prognostic guide.

The Immediate Cause of Death.—In one the immediate cause of death was sudden pulmonary edema in the seventh month of pregnancy; in 3 it was caused by pneumonia following delivery. One died suddenly twenty days post partum, probably from embolism (she had auricular fibrillation). One died from congestive failure six weeks post partum, and one from subacute bacterial endocarditis. However, the fatal cases do not reflect the experience of the prenatal clinic:

Case 1 was a private patient admitted to the hospital when almost at term. Case 2 was first seen by us the evening when she developed terminal pulmonary edema. Case 5 attended the St. Louis County Hospital, and was admitted to St. Louis Maternity Hospital for study only. She never attended the regular prenatal clinic. Case 6 was first seen by us when she was in the hospital with subacute bacterial endocarditis. Case 7 was a private patient and was not seen until she had developed pneumonia after delivery. Case 8 was first seen in St. Louis City Hospital and was referred to the Washington University Prenatal Clinic because of the great difficulties she presented.

Of these 8 fatal cases only Cases 3 and 4 belong to the regular series here under consideration, and of these Case 3 absented herself from the clinic during the crucial last trimester, against our expressed instructions. Case 4 was seen in the regular heart service several months before she became pregnant. She was there advised against conception, and given the proper instructions. These she neglected to carry out and as soon as her condition became known to the obstetric service (at twelve weeks), she was admitted to the Maternity Hospital. She responded so poorly to treatment that interruption was deemed imperative. She died from complications following the operation.

Thus it appears that among the regular patients with organic heart disease who followed our instructions and received adequate prenatal care from the beginning of pregnancy, there were no deaths.

Heart disease has been an important cause of death in St. Louis Maternity Hospital. Of 44 maternal deaths, 6 could directly be traced to valvular disease of the heart or its immediate complications. (Cases 6 and 8 died, not in the hospital, but still within six months of delivery, the period during which death may arbitrarily be considered to be connected with childbearing.) That is 13.6 per cent, somewhat higher than the average but in line with the experience of the Charity Hospital in New Orleans and the Boston Lying-in Hospital (Jensen p. 133). The 44 cases have been classified so as to compare with Jensen's Table XXVII.

TABLE VI

Sepsis	10
Toxemia	8
Obstetric complications (including hemorrhage)	9
Embolism	2
Acute infections (including pneumonia)	5
Heart disease	6
Other causes	4
	44

TREATMENT

The group of patients observed through clinic and hospital were managed in accordance with the principles now generally accepted, and discussed in detail by Jensen (loc. cit. Chapter 43). Obstetric patients were referred for medical-obstetrical consultation at the slightest suggestion of cardiac pathology. If heart disease was proved, considered probable or even possible, the patients were seen at regular intervals. Proved, but compensated, cardiac patients were seen every four weeks at first, then every three or two weeks and near term at weekly intervals. If, at any time, decompensation threatened, they were, because of shortage of beds at the Maternity Hospital, at first instructed to rest at home, but if such treatment was not promptly efficacious, they were admitted to the hospital until compensation was restored.

Unless decompensation threatened, patients were not admitted to hospital until onset of labor. The management of labor itself has changed somewhat at St. Louis Maternity Hospital during recent years and this change has also affected cardiac patients.

Cardiac patients are rarely given hyoscine. This drug quite uniformly causes a definite increase in heart rate which while it has no apparent ill effect on the normal patient might be objectionable in the cardiac. Barbiturates are used in a higher percentage of the cases than in the normal group, in many instances the barbiturate is being substituted directly for hyoscine in a morphine-barbiturate combination which is quite satisfactory when properly timed.

Local anesthesia fills an important place in selected cases for actual delivery. Infiltration with 1 or ½ per cent novocaine of either perineum or abdominal wall, depending on the route chosen, may fill the entire anesthetic need. In some of our cesarean sections on cardiac patients at the St. Louis Maternity Hospital, we have used nitrous oxide-oxygen inhalation, keeping well within a safe oxygen margin. In other cases a combination of local and inhalation anesthesia has been used, the inhalation being employed to supplement the local during the most painful part of the procedure (usually the actual extraction of the fetus results in sufficient discomfort to the patient to make from three to ten minutes of general anesthesia desirable). If this reaction on the part of the patient can be anticipated and the supplementary inhalation begun before any painful traction is made, the delivery can usually be accomplished quickly and without undue excitation of the mother.

A definite attempt is made to eliminate as much of the second stage of labor as possible in cardiac patients. This is done by the use of forceps applied as soon as the cervix is completely dilated and the head well down in the pelvis. Such a procedure spares the cardiac mother most of the dangerous stress and strain usually attending the forceful expulsive second stage efforts.

SUMMARY AND CONCLUSIONS

The experience from 1930 to 1938 of the Department of Obstetrics of Washington University with cardiac patients is analyzed. Patients with hypertensive or degenerative heart disease were excluded unless they also suffered from valvular disease of the heart. This material conforms fairly well with the general experience of the literature

when distributed according to age, gravidity, etiology of heart disease, anatomic lesions, and cardiac function. Of the patients admitted during this period to St. Louis Maternity Hospital, 8 died within six months of delivery from cardiac causes. Only two of these had been regular patients of the prenatal clinic, and on further analysis it was found that among the patients properly handled and cooperating with the clinic, there were no deaths. This experience leaves us convinced that while some cardiac patients should not become pregnant and should have their pregnancies interrupted if they do, the large majority of them can be carried successfully to term if given adequate prenatal care.

In St. Louis Maternity Hospital heart disease takes a place among the causes of death comparable to that which it takes in Boston Lying-in Hospital and the Charity Hospital in New Orleans.

Auricular fibrillation was rarely seen, but here as elsewhere, it was found to be a serious complication. The functional classification of the cases was similar to the general experience of the literature and its prognostic value was well borne out. However, this analysis failed to establish a correlation between cardiac enlargement as shown by x-ray records and cardiac function. In one case active rheumatic carditis prevented continuation of pregnancy. There was no evidence that patients with rheumatic heart disease are especially liable to eclampsia.

The treatment of these cases has been conducted along generally accepted lines, as far as we can see, with gratifying results.

ADRENAL CORTEX IN THE TREATMENT OF NAUSEA AND VOMITING IN PREGNANCY

J. KOTZ, M.D., F.A.C.S., AND MORTON S. KAUFMAN, A.B., M.D.,
WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, George Washington University Medical School)

THE use of adrenal cortex in the nausea and vomiting of pregnancy was suggested by Kemp in 1932. Kemp advanced the theory that there was a corticoadrenal deficiency in certain cases in the first trimester of pregnancy due to the failure of the adrenals to hypertrophy rapidly enough to compensate for the increased cortical demand. He based his theory on the following observations: (1) The maternal adrenal cortex undergoes hypertrophy during pregnancy. (2) First signs of corticoadrenal insufficiency in adrenalectomized animals are nausea and vomiting. (3) In Addison's disease, the earliest signs are anorexia and morning sickness, regardless of sex, and (4) post-mortem findings in hyperemesis, adrenalectomized animals, and Addison's disease are identical.

In 1933 Kemp reported a series of patients treated with adrenal cortex with excellent results, and in 1934 he added another group. Freeman, Melick and McClusky reported a series of 78 cases with only two failures in 1936. In spite of these favorable reports, this form of therapy has had no wide distribution in this country.

Since these reports were issued, the product has been refined and concentrated, and is now available in 5 min. capsules equivalent to ½ rat unit determined by the Grollman method, and in vials for subcutaneous and intramuscular injection in which each cubic centimeter is equivalent to 2½ rat units.*

METHOD

The therapeutic dose has been based on the severity of the symptoms. For the ordinary mild nausea of pregnancy, we have prescribed one 5 min. capsule three times daily, fifteen minutes before meals. For the more severe types, the capsules have been combined with daily injections of 1 c.c. of the liquid subcutaneously. Some of the previous authors have used the injections three times a day, but we feel that this method is unsuited to routine office practice, and is therefore impractical unless the patient is hospitalized.

The degree of nausea has been recorded as follows: + nausea only and/or occasional vomiting; ++ nausea, and vomiting three or four times a day; +++ vomiting of all ingested foods; and ++++ true hyperemesis, with regurgitated output greater than the intake.

We have used this type of therapy in 50 cases. The results are tabulated in Table I.

TABLE I. SUMMARY OF EFFECTS OF TREATMENT

	IMPROVED		UNIMPROVED	
DEGREE	CAPS. ALONE	CAPS. AND INJECTIONS	CAPS. ALONE	CAPS. AND INJECTIONS
+	13	4	3	
++	6	13		2
+++	2	4		2
++++		1		

RESULTS

In the first group, there were 20 patients, ranging in age from 19 to 38, with 12 primiparas and 8 multiparas.

It will be noted there were three failures using the capsules alone, and none using the combined therapy. It is possible that if these three patients had received injections, they would have been benefited. However, some patients refuse injections for the ordinary mild nausea, both because of the added expense and because of fear of injections. We had no such difficulty with the more severe cases.

In the second group there were 21 patients ranging in age from 22 to 36, with 9 primiparas and 12 multiparas. In this group there were two failures. Both of these patients received the combined therapy. One of these patients was influenced by strong psychic factors (Case 5), while the other patient had a history of severe hyperemesis at the preceding pregnancy. This patient stated that she was much benefited by the injections, and although she continued to be nauseated for about five months, the nausea was much less severe than with the preceding pregnancy.

In Group 3 there were 8 cases with two failures. The first patient (Case 4) received both capsules and daily injections for two weeks. A tentative diagnosis of chronic cholecystitis was made and this was later verified by x-ray. Following delivery, this patient has continued to have recurrent attacks of nausea and vomiting. The second patient also received capsules and injections daily for two weeks without

*These preparations have been supplied by the Difco Laboratories.

improvement. No organic pathology could be found to account for the symptoms, and they cleared up spontaneously at about the fifth month.

We have had only one case of true hyperemesis, since we have been using this form of therapy, and this case was referred to us. The patient was hospitalized and responded promptly to three injections of adrenal cortex. This patient (Case 3) was the only one in the series who received any additional form of therapy. She received the usual routine of sedation and intravenous fluids and glucose.

We feel that the decrease in the incidence of hyperemesis in our own cases has probably been due to the prompt treatment of the earlier stages with adrenal cortex.

The difficulty of evaluating any method of therapy in nausea and vomiting of pregnancy is readily apparent. Most cases of nausea and vomiting will clear up during the first trimester under any form of treatment, so that the fact to be determined is whether the recovery is more rapid than with other types of treatment. Another indeterminate factor is the psychic effect of capsules by mouth and hypodermic injections on a condition which has so large a psychic factor in it. To establish a basis for comparison we have tabulated the time elapsing from the last period to the end of nausea, and from the beginning of treatment to complete relief in Table II.

TABLE II. TIME ELAPSED UNTIL COMPLETE CESSATION OF SYMPTOMS

DEGREE	AFTER LAST PERIOD	AFTER BEGINNING TREATMENT
+	64 days	8.1 days
++	83 days	13.7 days
+++	92 days	17.5 days
++++	–	–

In the patients who responded to therapy, the results were often amazing. Many patients reported immediate improvement after taking three or four capsules. Those whom the capsules did not benefit were usually relieved by two or three injections. Most of these reported marked improvement after the first injection, and complete disappearance of symptoms after the third or fourth. Several patients stopped the capsules after the disappearance of symptoms, but were forced to return to them following a recurrence of nausea. The following case reports illustrate some of the results obtained.

CASE 1.—Mrs. M. S., gravida i, para 0, last normal period Dec. 5, 1938, was first seen on March 24, 1939. Nausea was ++. She received capsules on March 24 and one injection on March 25. Four hours after the injection the patient experienced complete relief from all symptoms and there have been no recurrences.

CASE 2.—Mrs. I. S., gravida ii, para i, last normal period March 6, 1939, was first seen on April 20, 1939. Nausea was ++. She received capsules three times a day for one week and daily injections for six days. She reported some improvement after the first injection, and the nausea was completely cleared up in one week.

CASE 3.—Mrs. H. M., para 0, gravida ii, last normal period March 6, 1939, was admitted to Sibley Hospital for hyperemesis gravidarum May 18. This patient was vomiting continuously whether food was ingested or not. She was markedly dehydrated. Acetone and diacetic acid were present in the urine. She was seen by us in consultation on May 19. The usual treatment for dehydration and acidosis was instituted and the patient was given 1 ampoule of adrenal cortex twice a day. After the third injection she stopped vomiting completely and the adrenal cortex was

discontinued. On her eighth day in the hospital, she had a slight spell of nausea and vomiting which was immediately cleared by an injection of adrenal cortex. She was discharged on the tenth day and has had no recurrence.

On the other hand, in many cases there are undoubtedly organic factors that are not benefited by this particular therapy. In others there may be psychic factors beyond our control. And in others, even though no organic or psychic pathology is found, the treatment seems to have little effect. A few of these cases are illustrated.

CASE 4.—Mrs. K., para i, gravida ii, last normal period October 25, was first seen on December 12. Nausea was +++. She received adrenal cortex by mouth for one month and received 15 daily injections of adrenal cortex. There was no improvement. The nausea and vomiting persisted to a greater or less degree throughout the entire pregnancy, but disappeared following delivery. An x-ray of the gall bladder showed poor function. We feel that this is a chronic cholecystitis aggravated by pregnancy.

CASE 5.—Mrs. M. L., para 0, gravida ii, last normal period Nov. 18, 1938, was first seen in my office on Feb. 20, 1939. This patient had a premature baby which died shortly after birth at her first pregnancy. During her second pregnancy, she continued to vomit in spite of treatment until she was assured that the baby was viable. The vomiting immediately cleared up and there has been no recurrence.

Because of the variety of factors concerned, we feel that the only criteria of therapeutic value is the impression of the clinician. It is our impression that adrenal cortex in the treatment of the nausea and vomiting of pregnancy is a distinct advance. The response to this form of treatment is usually prompt and often spectacular. Further study of larger numbers of cases should produce more conclusive data.

CONCLUSION

We feel that our results, using adrenal cortex by mouth and injection, are better than with any of the previous forms of treatment, including sedatives, antispasmodics, and other endocrine preparations. Treatment of severe vomiting with acidosis should still include measures for relieving these conditions, and sedation is still a valuable adjuvant to the treatment. However, adrenal cortex by mouth and by injection seems to be curative therapy in many cases.

SUMMARY

1. Fifty cases of nausea and vomiting of pregnancy treated by adrenal cortex orally and subcutaneously have been reported.

2. Though the therapeutic effect is difficult to evaluate, we feel that most of the patients were markedly benefited by this form of treatment.

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1835 EYE STREET, N. W.

BILATERAL OVARIAN DERMOIDS COMPLICATING PREGNANCY TREATED BY BILATERAL OOPHORECTOMY

C. J. ANDREWS, M.D., F.A.C.S., RICHARD B. NICHOLLS, A.B., M.D. F.A.C.S., AND AURELIA GILL NICHOLLS, A.B., A.M., M.D.
NORFOLK, VA.

(From Department of Obstetrics and Gynecology, Norfolk General Hospital.)

THE purpose of this paper is to report upon a rare and interesting obstetric complication, namely, bilateral ovarian dermoids complicating pregnancy, in which bilateral ovariotomy was performed at three months' gestation, and the patient was delivered spontaneously at term. According to the available literature, 43 cases of bilateral dermoids complicating pregnancy have been reported, of which 12 were noted in the first three months of gestation. We also present a summary of the treatment used in these reported cases and the best method of management for the particular period of gestation, including a discussion of the endocrinologic and surgical aspects.

Our interest was first aroused in the subject by a personally observed case. Its rarity was suspected, but our investigation of available literature on the subject was stimulated by the timely appearance of a similar case report of Bernard Notes,[1] in which he states that his review of the literature revealed only three other cases.

CASE REPORT

Mrs. A. H. W., aged 33 years, first consulted us on Oct. 26, 1936, stating she was anxious for a child by her second marriage. She had one child by her first marriage, had been widowed twelve years, and had been remarried one year. Family history was irrelevant. On Jan. 11, 1935, she had a pelvic examination which was negative; on June 5, 1935, a cyst was noted upon the right ovary. An acute pyelitis attack with pus in the urine, fever, and a white blood count of 13,000 responded to hospitalization. X-ray of the left kidney revealed a shadow in the left ureter which might be a stone. On Oct. 28, 1935, symptoms characteristic of the passage of a calculus from the left kidney to the bladder were noted, without blood and with little pus in the urine. On Oct. 17, 1936, because of severe pain in the lower left quadrant of abdomen and vomiting for about seven hours, the patient was examined at the Baltimore General Hospital, with the following observations recorded: tenderness without rigidity in the left lower abdominal quadrant; a bilateral tuboovarian mass, larger on the left, tender on the left only; white blood count 8,000 with 78 per cent polymorphonuclears; urinalysis negative. A diagnosis was made of chronic bilateral tuboovarian abscess, with an acute flare-up on the left side. Recommendations were, urogram and cystoscopy to be followed, if negative, by laparotomy.

Our findings nine days later, Oct. 26, 1936, were: an irregular, tender, doughy mass of the left adnexa, about 5 cm. in diameter, and a small cystic mass in the right adnexa. At that time a tentative diagnosis of left salpingitis, right ovarian cyst, and possible ectopic pregnancy was made. A Friedman test was negative. Six Elliott treatments gave slight relief and the left mass decreased in size.

Urogram made at the Norfolk Naval Hospital, Jan. 27, 1937, showed a triangular shaped shadow of calcium density in the lower left ureter about two inches above

the ureterovesical junction. On Feb. 20, 1937, a catheter with wax tip bulb was passed through this ureter without difficulty and without showing any scratches.

On May 1, 1937, the patient reported that her last period was Feb. 10, 1937. There was a slight vaginal bleeding for some time, but this had ceased. A Gilfillen skin test indicated pregnancy. No Friedman test was made. Fifteen days later she complained of lower abdominal pain with a small amount of vaginal bleeding. Our findings were: Uterus approximately size of six weeks' pregnancy, cervix not dilated, small amount of uterine bleeding. She refused all treatment, stating that she preferred miscarriage to the possibility of an abnormal fetus. On June 5, 1937, she returned, complaining of the same symptoms (vaginal bleeding, staining, and lower abdominal pain). Examination showed: Uterus developing normally and the size of a three months' gestation, and a mass in the cul-de-sac which was soft and doughy in consistency. We advised operation because of our diagnosis of extrauterine tumor complicating pregnancy.

On June 8, 1937, laparotomy was done and disclosed cysts of both ovaries, which appeared to be dermoids. Bilateral salpingo-oophorectomy and appendectomy were performed. Both cysts were posterior and filled the cul-de-sac. The undisturbed enlarged (two and one-half months) uterus contained an apparently normal intrauterine pregnancy. The dermoid cyst of the right ovary was three and one-half inches in diameter and nonadherent; the left was two inches in diameter and adherent to the left pelvic wall and cul-de-sac. The appendix had dense adhesions to the posterior surface of the cecum. The pathologic report read: (1) Dermoid cysts of both ovaries, (2) slight fibrosis of both oviducts, (3) normal appendix.

The patient's convalescence was uneventful and she was discharged on the twelfth postoperative day. The only endocrine therapy given was prolutin (progesterone), 1 international unit intramuscularly on June 8, 9, 11, 13, 15, 17, 19, and 21, 1937. Postoperatively the patient showed no disposition to vaginal bleeding or of the former uterine discomfort. Her prenatal course henceforth until delivery on Dec. 5, 1937, one hundred and eighty days after operation, was entirely normal. She was delivered spontaneously after a rapid and precipitous labor (first stage three hours; second stage twenty minutes; third stage four minutes). There was no abnormal bleeding or disposition of the uterus to relax. Lactation was established normally on the third day and the patient left the hospital on the tenth day, following a nonmorbid puerperium. Her breasts had dried spontaneously on the fifth day postpartum.

The routine six weeks' discharge examination on Jan. 21, 1938, revealed a perfectly normal pelvis except absence of adnexa. The patient reported that she had had one day of bleeding since leaving the hospital, and this had subsequently been followed by amenorrhea.

In contrast to the four cases reported by Notes,[1] we were able to find 43 cases, including his own, of this obstetric complication, reported in the literature available to us. A series of 19 cases from the literature before 1911 was reported by Manton. Manton did not specifically list these cases by author and publication. We are, therefore, unable to determine how many of his series are contained in ours.

Table I states the author and the number of bilateral dermoid cysts complicating pregnancy reported in each instance. It presents sufficient cases to show that bilateral ovarian dermoids complicating pregnancy are not as rare as the authors had thought after reading recent reports of such cases. In spite of its rarity this complication of pregnancy is of great consequence.

A consideration of the best treatment of this complication of pregnancy as gleaned from this series presented endocrinologic and surgical problems of management. Let us first consider the surgical aspect. The series of bilateral dermoids was not sufficiently large to warrant

TABLE I

AUTHOR	CASES OF BILATERAL DERMOID CYSTS	COMPLICATING PREGNANCY
1. Bantock[35]	1	Yes
2. Kosminski[36]	1	Yes
3. Nystrom, E.[37]	1	Yes
4. Rausch, Z. W.[38]	1	Yes
5. Schockaert, R.[39]	1	Yes
6. Levy-Solal, E.[40]	1	Yes
7. Faure, J. L.[41]	1	Yes
8. Notes, Bernard[1]	1	Yes
9. Gellhorn, George[42]	1	Yes
10. Wells, H. Brooks[43]	1	Yes
11. Manton, W. P.[3]	1 of his own, 19 before 1911 from literature	Yes (but diagnosed after delivery) 9 mo.
12. Campbell, Malcolm[44]	1 of his own	Yes
	1 of Page, F.	Yes
	1 of Thornton Knowsley	Yes
	1 of Mattei	Yes
	1 of Schroder	Yes
	1 of Terrier	Yes
13. Waldstein[23]	1	Yes
14. Matthews, Frank S.[45]	4	Yes
15. Campbell[46]	1	Yes
16. Levy, Suzanne[47]	1	Yes
17. Idem. Case[48] of M. Faure, reported as "Obs. 11"	1	Yes (full term)
18. Idem.	1	Yes
19. Idem. Case of Munde, Obs. 8	1	Yes
20. Runeskog, B.[49]	1	Yes
21. Abruzzese, C.[50]	2	Yes
22. Duncan, Perry E.[51]	1	Diagnosed 4 mo. after abortion
23. Stropeni, L.[52] (Cases of Horrmann, 1911)	1	Yes
	2	Yes
24. Loewy, R., and Gueniot, P.[53]		
Case of Chantreuil[54]	1	Yes
Case of Flaischen (1892)	1	Yes
Case of Galabin[55]	1	Yes
Case of Braum (1892)	1	Yes
Case of Mangin[56]	1	Yes
Case of Merse (1896)	1	Yes
Case of Cortiguera (1895)	1	Yes
25. Deletrez[57]	1	Yes
26. Delporte[58]	1	Yes

conclusions relative to bilateral ovariotomy performed during gestation, so we decided to investigate the available literature on this point. We found that removal of both ovaries in the early months of pregnancy is a comparatively uncommon occurrence and slightly more unusual is the continuance to term of the pregnant woman in whom a bilateral oophorectomy has been done in the third month of pregnancy. In addition to our case, 12 in the first three months' gestation, in which bilateral oophorectomy was done, are described in the available liter-

TABLE II

AUTHOR	PERIOD OF GESTATION AT WHICH OPERATION WAS PERFORMED	OUTCOME OF PREGNANCY
1. Bantock[35]	Bilateral ovariotomy; period of gestation, third month	Delivered at full term
2. Dsirne[60]	Reports five cases bilateral ovariotomy but time of operation in each is not given	All delivered at term
3. Essen-Moller[61]	Bilateral ovariotomy; period of gestation, fourth week	Delivered at full term (260 days), after operation
4. Rausch, Z. Weifel[38]	Bilateral ovariotomy, 43 days of gestation	Aborted 15 days post-operative
5. Schockaert, R.[39]	Bilateral ovariotomy, fifth month gestation	Full term, normal delivery
6. E. Levy-Solal[40]	Bilateral ovariotomy, ninth month gestation	Cesarean section successful
7. Faure, J. L.[41]	Bilateral ovariotomy, 6 weeks' gestation	Full term, normal delivery
8. Notes, Bernard[1]	Bilateral ovariotomy, 3½ months' gestation	Labor induced successfully 2 weeks before full term
9. Wells, H. Brooks[43]	Bilateral ovariotomy, 4 months' gestation	Term
10. Campbell, Malcolm[44]	Bilateral ovariotomy, third month	Full term normal delivery
11. Campbell, Malcolm[44] (Case of Thornton Knowsley)	Bilateral ovariotomy in fourth month	Full term 5 mo. 19 days after operation
12. Eiss, Stanley[19]	Bilateral ovariotomy, fourth month	Normal childbirth
13. Wilson, Karl M.[6]	Removal of only ovary present in patient at 5 weeks	Abortion 5 days after operation
14. Waldstein[23]	Bilateral ovariotomy two months	Term
15. Matthews, Frank S.[45]	Case 1, removal both ovaries and uterus, 1 month	Surgical abortion
16. Levy, Suzanne[47] (Case of J. L. Faure) Obs. 1	Bilateral ovariotomy, third month	Full term, normal delivery
17. Idem. (Case of M. Faure) Obs. 2	Bilateral ovariotomy, third month	Full term, normal delivery
18. Idem. (Case of Galabin) Obs. 5	Bilateral ovariotomy, fifth month	Full term
19. Idem. (Case of Mangin) Obs. 6	Bilateral ovariotomy, second month	Delivery at full term

TABLE II—CONT'D

AUTHOR	PERIOD OF GESTATION AT WHICH OPERATION WAS PERFORMED	OUTCOME OF PREGNANCY
20. Idem. (Case of Bernard) Obs. 7	Bilateral ovariotomy, third month	Aborted fourth postoperative day
21. Idem. (Case of Munde) Obs. 8	Bilateral ovariotomy, 6 months	Aborted
22. Idem. (Case of Sutton)	Bilateral ovariotomy. Gestation not given	Twins at term
23. Idem. (Report of Perier on case of Mouchet) 1897	Bilateral ovariotomy	
24. Idem. (Case of Polaillon)	Bilateral ovariotomy, 4 months	Full term normal delivery, normal child
25. Idem. (Case of Bantock, from Rev. de Pozzi, Obs. 4)	Bilateral ovariotomy, 3 months	Full term
26. Idem. Braun (Case in Rev. de Pozzi) Obs. 9	Bilateral ovariotomy, 5 months	Aborted fourteenth day postoperative
27. Idem. (Case of Cortiguera in Rev. de Pozzi)	Bilateral ovariotomy	Aborted
28. Idem. (Case of Merse in Rev. de Pozzi)	Bilateral ovariotomy, ninth month	Full term, normal
29. Polichetti, E.[59]	Bilateral ovariotomy, 6 weeks' gestation	Full term, normal delivery, normal fetus
30. Loewy, R., and Gueniot, P. (Case of Flaischen)[53]	Bilateral ovariotomy, third month of gestation	Full term, normal delivery and fetus
31. Galabin[55]	Bilateral ovariotomy	Not full term
32. Deletrez[57]	Bilateral ovariotomy, fourth month	Full term
33. Stropeni, L.[52] (Cases of Horrmann) (2)	1. Bilateral ovariotomy, second month	Aborted
	2. Bilateral ovariotomy. Period of gestation not given	Full term
Stropeni	Bilateral ovariotomy, fourth month	Full term, normal

ature; 10 delivered normally; 2 aborted. As a basis for our conclusions on surgical treatment we present Table II, showing the source, the month of gestation at which operation was performed, and the outcome of the pregnancy. These cases are grouped not because of their common etiology, but because each had surgical treatment, bilateral ovariotomy, performed during pregnancy.

DISCUSSION

Possible complications of bilateral dermoid cysts have led to a more or less general agreement among obstetricians that the cysts should be removed during preg-

TABLE III. TIME OF OPERATION AND OUTCOME

	MONTH	CASES GIVEN	ABORTIONS
Part 1:	Taken from McKerron[22] and concerns cases in which corpus luteum was removed		
	Second	5	18.5%
	Third	5	8.8%
	Fourth	3	5.3%
	Fifth	2	6.2%
	Sixth	4	22.2%
	Seventh	3	20.0%
	Eighth	4	57.1%
	Ninth	0	0.0%
Part 2:	Taken from M. Erik Ask-Upmark[27] and concerns cases of corpus luteum removed		
	First and second	16	25.0%
	Third	18	11.0%
	Fourth	17	12.0%
	Fifth	14	28.0%
	Sixth	2	50.0%
	Seventh	2	50.0%
	Eighth	8	25.0%
Part 3:	Taken from Table II of this paper (bilateral ovariotomies)		
	First and second	6	33⅓%
	Third	7	14$\frac{2}{7}$%
	Fourth	7	0.0%
	Fifth	3	33⅓%
	Sixth	2	50.0%
	Seventh	1	100.0%
	Eighth	0	0.0%
	Ninth	1	0.0%

nancy. Briefly stated, the possible complications are: the dangers of cysts becoming malignant epitheliomas during pregnancy;[18] the greater danger of torsion of the pedicle and gangrene of the cysts in gravid women;[18] suppuration of the tumors;[18] mechanical interference with labor;[21] malpresentation and uterine inertia;[24] hemorrhage into the tumor;[24] rupture of dermoids with an associated chemical peritonitis.[23, 20] Since there is a possibility of the occurrence of any or all of these complications at any time during gestation and since it is not endocrinologically necessary (see discussion later), we do not agree with that small minority of authors who maintain that ovariotomy should be done at term and the patient delivered from below subsequent to the operation.[25] The results noted in the tables convince us that, as to the treatment in the early months, we agree with Frank;[26] namely, it is better to postpone laparotomy and removal of the dermoids until after the corpus luteum (at least four to six weeks) is no longer necessary, unless an acute surgical condition demands an immediate operation. Study of results warrants the conclusion that the fourth month is the optimum time for surgical treatment. This is in accord with the conclusion of Levy,[18] of McKerron,[22] and of Lynch.[20] If the diagnosis is made shortly before viability, the evidence recommends "watchful waiting" until the fetus becomes viable, at which time operation is accompanied by cesarean section. Thus, the paramount question in surgical treatment concerns time and type of operation.

Concerning the type of operation, we believe that ovariotomy or resection is best decided at the time of laparotomy. The ideal, of course, is to conserve as much normal ovarian tissue as possible. There is a divergence of opinion relative to the removal of the tubes. Some believe this is more likely to cause abortion. This was not true in our case, and we believe that the oviduct should be removed

if chronically diseased or if double ovariotomy is done. We were not able to find in the literature available to us sufficient evidence of tube removal causing abortion to justify our leaving them routinely.

It is interesting to note in passing that Pucel[28] and Heils[29] report 16.5 per cent and 19.47 per cent of abortions, respectively, following operative procedure, while Remy[30] finds 17 per cent abortions without any operative interference whatever. The dangers of complications outweigh the dangers of abortion if these findings justify any conclusion.

Let us consider next the endocrinologic aspects of management. We have implied above that the corpus luteum played a part in our conclusion as to the optimum time of operation. A review of recent articles concerning this gland will show us why this is true, and possibly what endocrine therapy is needed postoperatively to encourage a normal gestation and delivery.

According to Wolf,[4] the luteinizing function in the human being is maintained after the first half of pregnancy solely by the placenta and the pituitary and injections of progestin can prevent habitual abortion by keeping the uterine musculature quiet. This is in keeping with the classical observations of Fraenkel, Loeb, and Ancel and Bouin, which established the corpus luteum as an endocrine gland whose primary function was to prepare the uterus for implantation of the fertilized egg.[31] Wilson[6] sums up the evidence in human beings by saying: "While in general the corpus luteum is necessary for the proper maintenance of pregnancy in the early months, the duration of the time that this necessity exists varies with individuals." Individual variations are always a safe hypothesis in medicine never to be minimized; but for practical clinical purposes we attempt to arrive at the general normal for the initial approach to treatment or management and to subsequently individualize it. Pratt,[7] commenting on Wilson's paper, describes one clear-cut illustration of a normal human pregnancy without the presence of a corpus luteum after the beginning of nidation (twenty-one days after onset of patient's last menstrual flow). Pratt and others[8] state: "Indications for the therapeutic use of progestin for treatment of abortion are theoretically speculative."

That the placenta and corpus luteum contain the same hormone has been proved, for recently progestin has been found in human placenta (Mazer and Goldstein, 1932; Adler, de Fremery and Tausk, 1934; Ehrhardt, 1934; McGinty, McCullough and Walter, 1936; Ehrhardt and Fischer-Wasels, 1936; Smith and Kennard,1936[31]). The progestational substance has been extracted from the original extract which also contained an estrogen fraction (Allen and Myer, 1933) and the structural formula of progesterone ascertained (Butenandt, May, 1934; Slotta, Ruschig and Fels, July, 1934; Allen and Wintersteiner, August, 1934; and Hartmann and Wettstein, 1934[31]). The performance of bilateral ovariotomy with noninterference with gestation and delivery fits in with the concept of the presence of progestin in the placenta.

It was shown by Allen, 1930, Hisaw and Leonard, 1930, that the previous influence of the estrogenic hormone was needed to make it possible for progesterone to produce its progestational changes in the endometrium. This synergistic action of estrogen and progesterone is further shown by the more recent experiments of Allen and Heckel. Their work makes it evident that for progesterone to have any visible effect on the structure of the uterus, it must be given to an animal which has recently been under the influence of estrogen, and if its effects are to be maintained for more than a short time, estrogen must be given with progesterone. The efficacy of progesterone, or of progesterone and estrogen in combination, in maintaining human pregnancy, has not been extensively or thoroughly investigated.[31]

Jones and Weil[9] report a case in which the corpus luteum was removed on Oct. 28, 1937, and who subsequently delivered a normal, living child on June 27, 1938. In this case they observed that no pregnanediol was present in the urine for about twelve days after removal of the corpus luteum. It then reappeared in increasing amounts. Their conclusion was that pregnancy can survive in the human being after the withdrawal of progesterone, or that it can survive on

quantities of progesterone too small to produce pregnanediol in quantities sufficiently large to be determined by the method employed. They further state that the placental production of progesterone, at least in one case, begins about the second month, i.e., about the time (sixtieth day) that Browne and Venning[10] and later Evans and others[11] found the maximum gonadotropic substance occurs in pregnancy. Obviously, the appearance of such large quantities in pregnancy, at a time when the ovaries can be removed in the human being without miscarriage (Tables II and III) further supports the conclusion that progesterone is not only found in the placenta, but it is elaborated in it. This is not in accord with the findings of Collip and Campbell,[13] who believe they have shown that the placenta does not produce a corpus luteum hormone but that it manufactures three other hormones: (1) one corresponding to folliculin; (2) one corresponding to the so-called prolan A. and (3) one corresponding to prolan B.

The outstanding difficulty met in these investigations concerning the chemistry of the maintenance of pregnancy is that the tests used most frequently in the clinical practice are urine tests for the metabolic product of the hormone, pregnanediol glucuronide, rather than for the specific hormone content of the blood. Hamblen and associates (1939) list in detail the four factors which are concerned in the excretion of pregnanediol, thus complicating the interpretation of urinary findings. Allen (1939) reports a new and more sensitive method for the bioassay of progesterone, based upon blood specimens.[31]

We believe the above experimental evidence points to the placenta, after sixty days, as the chief custodian of the preservation of pregnancy endocrinologically in the human being. This does not clear up the rationale of using progestin in the case of threatened abortion for its pharmacologic action (uterine sedation) or as a possible adjunct to an inadequate corpus luteum in the early months of gestation, or as a possible adjunct to an inadequate placenta after sixty days of gestation. Experimental evidence in animals would suggest that in the case of the last, estrogen should be given with progesterone. Before this type of therapy can be scientifically administered, more studies are needed during pregnancies to determine the normal for blood and for urine at stated time intervals.

A start in this direction has been made by Stover and Pratt,[33] 1939, and Rakoff,[34] 1939. Likewise, once the normals are determined, urinary and blood studies on patients with threatened abortion may serve as a guide to the administration of progesterone and estrogen and their indications in threatened abortion be clarified. The advantage of progesterone over other uterine sedatives is at this time questionable; not to mention comparatively expensive.

These studies might help to solve the riddle of pre-eclampsia, since the excretion of pregnanediol has been reported to be low in such patients (Weil, 1938; Smith and Smith, 1938); although the explanation may lie in liver dysfunction, one of the factors involved in the findings of Hamblen and others,[32] 1939.

To continue with the endocrine implications of the case reported by us, the precipitous labor of our case would suggest that folliculin in the mechanism of normal labor may not be necessary in human beings, or it may be supplied by some other organ. These observations are in keeping with the experimental findings of Collip and Campbell,[13] namely, that the placenta manufactures a hormone corresponding to folliculin. We were unable to ascertain the normalcy of lactation in many of the cases of bilateral oophorectomies reported in the literature. Lactation was spontaneously absent after the fifth day post partum in our case. We wish to emphasize that this in no way essentially contradicts the findings of S. Levy,[18] that in spite of double castration the puerperium may be normal.

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605 Medical Arts Building

Munoz, Hector Cruz: Hyperplasia of the Endometrium Following Operative Procedures on the Ovary, Bol. Soc. chilena de obst. y ginec. **4:** 71, 1938.

The author reviews the literature and reports two cases of hyperplasia of the endometrium following operative procedures on the ovary. He concludes that the gynecologic operations which more or less considerably reduce ovarian tissue may produce hyperplasia of the endometrium with typical hemorrhage. The anatomic alterations found in these cases are identical with those encountered in laboratory animals.

Mario A. Castallo.

STUDIES ON PRESERVATION AND USE FOR TRANSFUSION OF PLACENTAL BLOOD

CHARLES S. FINE, M.D., ROBERT L. ALTER, M.D., AND ARTHUR BAPTISTI, JR., M.D.,* BALTIMORE, MD.
(From the Baltimore City Hospital)

THE therapeutic use of blood transfusions plays an important role in modern medicine, particularly in the emergencies of obstetrics. Suitable donors, however, are not always available, so that attention was focused on the problem of the preservation of human blood and following diligent investigation, particularly by the Russians, the modern blood bank has been evolved.

In 1938, Goodall and his co-workers reported a method of collecting and preserving placental blood with its subsequent use for transfusion in adults. The reported results sounded like the actual fulfillment of every obstetrician's dream. By using the blood preservative of the Moscow Institute of Hematology, Goodall reported that the blood could be kept practically indefinitely and given without fear of any reaction and, moreover, he assumed the biologic significance of fetal blood to be even greater than that from adult donors. Subsequently, several other clinics have attempted to confirm Goodall's results, and although the procedure seemed to have possibilities, their enthusiasm apparently did not equal Goodall's.

The procedure has been given a careful test at the Baltimore City Hospitals. On the Obstetrical Division, about 200 service cases are delivered each month in the hospital so that ample clinical material was available.

METHODS AND RESULTS

We repeated the method of collection as described by Goodall; that is, by milking the blood out through the sterilized severed end of the cord into a sterile flask which contained the preservative solution—the placenta remaining in utero. Those cases in which the child was premature, the membranes prematurely ruptured, the uterine cavity infected or the blood Wassermann reaction positive, were not used. The average amount of blood collected from such selected placentas was 70 c.c., although Goodall reported an average of over 100 c.c. A specimen of blood was also collected in two separate tubes for grouping and Wassermann tests. The flasks were stored in an ice box with a constant temperature of 36° F. Eight specimens were immediately cultured upon collection. These cultures were done on beef heart infusion agar (pH 7.8) poured plated and on beef heart infusion peptone broth (pH 7.6). These cultures were all negative and the same specimens proved to be negative on re-culture five days later on the same type media. In order to determine the bactericidal action of the preservative, original specimens known to be negative were intentionally contaminated with *Bacillus coli, Staphylococcus albus, Staphylococcus aureus,* and *Bacillus subtilis.* These specimens were kept in the ice box for four days and recultured. Those flasks containing *Bacillus coli* or *Staphylococcus albus* were sterile. *Staphylococcus aureus* was inhibited, but *Bacillus subtilis* flourished in the mixture.

At this stage of the work, it seemed safe to use the blood for transfusion so far as the bacteriologic evidence was concerned. Accordingly, 4 transfusions

*With the technical assistance of Arthur Ballantyne.

were given to patients who were afebrile but who had low hemoglobin values postpartum, in amounts ranging from 150 to 250 c.c. All 4 patients had severe reactions which took the form of a chill followed by a temperature rise to 103° or 104° F., pain in the back and extremities. In 1, the reaction set in before all the blood was given. In the other 3, it occurred within an hour of receiving the blood.

Since our yield was quite small and we had 4 consecutive reactions and thinking that perhaps certain unknown substances had passed into the blood while collecting it, we devised another method for collection. As soon as the child was born, the cord was clamped immediately as close as possible to the umbilicus and was severed between two clamps. The placenta was then expressed and was placed on a sterile towel on the instrument table. The cord was then milked down to within about 5 cm. of the base of the placenta and clamped once more. The cord and a portion of the placenta adjacent to it were cleansed with a mercuric chloride, or Scott's solution followed by alcohol. A sterile towel was placed over the clamp and empty cord adjacent to it. If the operator was collecting the blood, he would change his gloves. A No. 16 needle, to which was attached a two-way stopcock and a 50 c.c. or 100 c.c. sterile syringe, would then be inserted into the main vessel of the cord and the blood drawn into the syringe. The blood collected was then transferred to a sterile flask containing the preservative, a small amount being placed in an oxalate bottle for blood counting, hemoglobin determination, etc. The two-way stopcock was utilized to prevent the blood from escaping from the end of the inserted needle while it was being transferred. Only slight suction was necessary in order to draw the blood into the syringe. By this method, our yield averaged 87 c.c. It was advantageous from 2 aspects. One could inspect the placenta and by the size of the vessels and the placenta could determine whether the yield would be worth while. Second, by this method, the operator did not necessarily have to collect the blood, as someone standing by who knew the method could don a pair of sterile gloves and carry out the same procedure.

The majority of placentas used were those which were thought would give a greater yield than 70 c.c. However, included in our collections were some yields of 50 c.c., utilized when a large number of deliveries were productive of small placentas, and we were anxious to obtain blood.

Transfusions were then given in amounts ranging from 65 to 400 c.c. The preservative solution used was that devised by the Moscow Institute of Hematology, consisting of:

Sodium chloride	7.0 gm.	in 1,000 c.c. of distilled water. The amount of preservative used was 125 c.c.
Sodium citrate	5.0 gm.	
Potassium chloride	0.2 gm.	
Magnesium sulphate	0.04 gm.	

Thirty-six transfusions were given to adults with reactions similar to the above in 47 per cent of the cases. Six transfusions were also given to infants and children on the pediatric service with a questionable reaction in one. It was questionable because the patient had otitis media and pneumonia and was receiving sulfapyridine. On analysis the reactions could not be correlated with any controllable factor such as length of preservation, amount of blood and preservative, amount of hemolysis, speed of administration, or blood groups. Analyzing this in somewhat greater detail, the length of storage before giving the transfusions varied between one and twenty-four days (average six days). This made no difference whatsoever in this small series. Hemolysis was not a factor. Some of the bloods given were markedly hemolyzed and no reactions occurred. In fact, we noted that with this solution and others that we used, the rate and amount of hemolysis were variable factors. Hemolysis in some of the above blood used occurred in about twenty-four to forty-eight hours and in others, somewhat later. It was not referable to any appreciable extent on the ratio between the amount of blood and the preservative. Whether it was dependent on an individual variation of the cells themselves, it is difficult to be

certain. The amount of blood given could not be considered as a cause. Reactions were obtained in some cases when only 60 c.c. of blood had been given and the transfusion had to be stopped. One patient received 400 c.c. of blood at one time without a reaction. The patient was a Group II, with a ruptured uterus. She was given approximately 200 c.c. of her own group and 200 c.c. of Group IV, immediately after the Group II blood had run in.

Four patients received more than one transfusion. One of these received 3 and had 1 reaction, 1 received 2 and had reactions with both, and the third had 3 transfusions, with reactions in two instances. The fourth received 2 transfusions without reaction.

The cross matching was checked carefully by 3 different individuals. In order to establish a control regarding the preservative, 6 patients were given sterile preservative, without blood, intravenously and none of them had a reaction. This procedure was carried out in the same fashion as when blood was collected. The flasks were unwrapped from the sterile towel; opened, as if they were going to receive blood; plugged after an interval equal to the time it would take to collect the blood. It was then stored in the ice box for various intervals and then given to the patient. In 2 cases, preservative was given without untoward effect to patients who had had a reaction with placental blood.

Further studies were made in an attempt to ascertain the cause of reactions. Five transfusions of approximately 100 c.c. of blood from adult donors and 125 c.c. of the above preservative were given to patients and in only one a slight reaction occurred.

For control purposes, when feasible, the contents of one flask were used for transfusion as we were anxious to observe the effects of storage, hemolysis, etc. When several flasks were used, the bloods used were as nearly as possible similar as to storage time, hemolysis, etc.

The hemoglobin rise in most cases was satisfactory. The average rise was 7 per cent in three days and at the end of five days, the average rose to 11 per cent. However, these figures are not conclusive, as the amounts given varied somewhat. Phenomenal rises occurred in some cases; in one instance a 20 per cent increase was noted on the third day. And by the fifth day, 3 patients, excluding the above, had had an increase in hemoglobin value as much as 22 per cent. It is difficult to correlate the increase in hemoglobin values with the hemoglobin content of the placental blood, red blood count, the time of storage, and other factors in such a small series. But we can say with reasonable certainty that this blood does give a satisfactory rise in hemoglobin value and in some cases it is phenomenal. Perhaps the correction of the dilution phenomena of pregnancy during the puerperium may play some part.

Although we had previously satisfied ourselves as to the sterility of the blood given at this stage, we felt that this should be checked once more in view of the number of reactions. Consequently, immediately before giving a transfusion, a small amount of blood was transferred to a small sterile flask for culture on the same media as previously used. Seventeen consecutive cultures were sterile. Reactions occurred in 25 per cent of these 17.

Recent investigation by DeGown and others, indicates the advantages of a modified Rous-Turner preservative consisting of: 5.4 per cent glucose, 13 parts; 3.2 per cent sodium citrate, 2 parts; and blood, 10 parts.

We collected blood in the usual fashion and gave 6 transfusions using this solution as a preservative, removing samples as usual for culture immediately before giving the blood. The minimum time that this blood had been stored was one day, and maximum five days. None of these patients had reactions, but within twenty-four hours, we had luxuriant growths of *Bacillus fecalis alkaligenes*, 30 to 100 colonies per c.c. The blood had been planted on the same media as used previously, beef heart infusion agar poured plates and beef heart infusion peptone broth. These patients were watched carefully but all of them had normal temperature curves during their hospital stay. They were checked again one month after leaving the hospital and all felt well.

We, of course, then ceased giving transfusions but still collected blood, trying to perfect our technique. Seven per cent iodine was substituted for the mercuric

chloride without any effect. Seventeen consecutive cultures, with the glucose citrate as a preservative, were positive for *Bacillus fecalis alkaligenes* with the number of colonies ranging from 15 to 200 per c.c. The time interval between collection and culturing varied from twelve hours to five days, average forty-eight hours. Hemolysis was quite marked with this preservative, usually occurring in twenty-four hours and gradually increasing. With this solution and with our previous solution, clotting also occurred to some extent, but this was a variable phenomenon as to time and amount.

Our conclusion was that the glucose enhanced the growth of these organisms, and we then decided to use 15 c.c. of a 5 per cent sodium citrate solution as a preservative and carry out further cultures, using 7 per cent iodine and 95 per cent alcohol to clean up the cord. Six samples of blood were then collected and cultured with the previous media and one positive culture was obtained; the rest were sterile. No reactions were obtained, using this blood in amounts ranging from 95 to 100 c.c. The blood was given after a storage time of three to four days. Hemolysis was slight in this period of time, but the blood was very thick so that it was necessary to dilute it with normal saline in order for it to pass through a sterile gauze filter. One patient received blood which subsequently grew organisms. The reason that this blood was used was due to the fact that we had had such rapid growth with the glucose solution, usually in twelve to fourteen hours, that we thought that if the bloods were positive for this organism it should appear in at least twenty-four hours. No growth had occurred with any of these blood samples in twenty-four hours; we then went ahead and transfused the 6 patients mentioned, only to find out that on the following day, colonies had begun to appear in the one culture.

At this stage, it was apparent that the glucose had enhanced the growth of these organisms and that the preservative was an excellent medium. We were now anxious to know what, if any, of the constituents of the Moscow solution would have a bactericidal or bacteriostatic effect and counteract the presence of glucose.

A solution consisting of 5.4 per cent glucose, 13 parts, and 3.2 per cent sodium citrate, 2 parts, was made up and to a liter of this was added 0.04 gm. of magnesium sulphate and 0.2 gm. of potassium chloride—the same amount of these constituents as was present in the Moscow solution. We had omitted sodium chloride and changed the proportion of sodium citrate.

Six consecutive blood samples were then collected carefully in the usual fashion, using iodine and alcohol to clean up the cord, and all 6 were positive for *Bacillus fecalis* in less than twenty-four hours. These had all been stored previously in the refrigerator from two to four days.

The problem that now confronted us was how to obtain sterile blood. It also occurred to us that perhaps originally, with the Moscow solution and the 5 per cent sodium citrate solution, positive cultures would have been obtained had we used glucose in the media. Consequently, we began to culture all collections with a special medium consisting of (1) beef heart priptose agar which contains 1 per cent glucose (pH 7.3) and (2) beef heart protease agar (pH 7.2). With the latter, when pouring the plates, 2 c.c. of a sterile 10 per cent glucose solution were added. In addition, cultures were also made with beef heart infusion protease broth (pH 7.4), containing 1 per cent glucose.

We then collected twelve samples of blood. In 6 of these, the preservative used was 20 c.c. of a 5 per cent sodium citrate solution and in the remaining six 50 c.c. of a 1.5 per cent sodium citrate solution in normal saline. Not knowing the exact source of these organisms and attempting to eliminate contaminants from the surface of the cord, that portion where the needle was to be inserted as well as a portion of the surrounding placenta was cleansed vigorously with green soap, ether, alcohol, and 7 per cent iodine, followed by alcohol once more. These samples were stored for two to four days, and then cultured with the new medium and all were strongly positive for *Bacillus fecalis alkaligenes*. In fact, in 6 of these, in addition to the above clean up, concentrated nitric acid was applied to the area where the needle was to be inserted and then washed off with alcohol, without any better results. Six samples of blood were also collected, using the

Moscow solution as a preservative, stored for two or three days and then cultured. Positive cultures of *Bacillus fecalis* were obtained in all 6.

Grodberg and Carey recently reported a series of 75 transfusions with placental blood at the Boston City Hospital. Their method of collection was similar to that of Goodall except for some minor details. They reported that very few of their bloods collected gave positive cultures. At the time of collection, a sample of blood was cultured on plain broth, without glucose, similar to our original cultures.

It was thought at this time that perhaps the passage of the placenta through the vagina and the handling of the placenta in some fashion increased the number of bacteria in the blood. We were also anxious to collect blood in a similar manner as was done in Boston and to see whether by our new medium positive cultures could be obtained. Accordingly we collected ten samples of blood from the cut end of the cord, cleaning the cord with iodine and alcohol and severing it with sterile scissors. Culturing these collections with the new medium, we obtained positive cultures of *Bacillus fecalis* in 9 out of 10. The preservatives used were 20 c.c. of 5 per cent sodium citrate in 5 and 50 c.c. of 1.5 per cent sodium citrate in normal saline in the other five. We must say, however, that growth was moderate and took twenty-four to forty-eight hours to appear on the plates. The blood was kept in the refrigerator from two to three days before planting it on the medium—average collection was 81 c.c.

Samples of blood stored for various intervals which were originally positive were now cultured once more. Six samples of blood were found to be sterile seven days after they were found to contain organisms. Others cultured ten, twelve, and sixteen days after being found positive were also sterile. The preservatives in the above were equal numbers of the various types. Moscow, 5 per cent sodium citrate, and 50 c.c. of 1.5 per cent sodium citrate in normal saline. Equal numbers of those collected by needle and syringe, and by the method of Grodberg and Carey, were sterile. It is quite possible that the blood was sterile a few days before we cultured it. In our previous studies *Bacillus coli* and *Staphylococcus albus* were apparently killed in four days.

Eight transfusions were then given in amounts ranging from 100 to 120 c.c., using blood which had previously contained organisms and now had been found to be sterile. The minimum time of storage was thirteen days, maximum twenty days. Preservatives used were 5 per cent sodium citrate, 20 c.c. and 50 c.c. of 1.5 per cent sodium citrate in normal saline, four of each. One severe reaction was obtained with a chill lasting twelve minutes and a temperature rise of 103° F. The blood used in this case had been stored thirteen days and was collected by the method of Grodberg and Carey. Observations on hemolysis revealed that the best preservative from this standpoint was the 1.5 per cent sodium citrate in normal saline. Hemolysis was slight with this preservative as long as twenty days after collection. The next best was 5 per cent sodium citrate solution, followed by the Moscow preservative and then glucose citrate mixture. There was, however, very little to choose between the latter two preservatives; both hemolyzed the blood much more rapidly than the first two mentioned.

An attempt was now made to determine the source of the organisms. Blood and surface cultures were taken from various portions of the placenta—6 placentas were used. The procedure was as follows: Immediately after delivery the cord was clamped as usual. It was then cleansed with iodine and alcohol. The cord was cut with sterile scissors and blood collected for culture. The cord was then clamped once more. It was cleansed again and a surface culture obtained. A needle was then inserted into one of the veins between two clamps and another sample of blood was obtained. The placenta was then expressed. The cord was clamped immediately about 3 or 4 cm. from its origin from the placenta. The surface of the cord where a needle was to be inserted and the adjoining placenta was cleansed as usual and another surface culture was taken from this area. A needle was then inserted, and another sample of blood withdrawn.

Our results were similar in all 6 placentas used. All surface cultures, taken before the cord and placenta were cleansed, yielded *Staphylococcus aureus, Staphylococcus albus,* and *Bacillus coli* with the exception of one, in which no growth

was obtained. All surface cultures taken after the cord was cleansed were sterile. Blood cultures whose sources were the cut end of the cord and from one of the veins before expression of the placenta yielded *Bacillus fecalis* in all. Blood cultures taken after the expression of the placenta also grew *Bacillus fecalis*. In the latter, growth was heaviest.

The indication was that the blood from these 6 placentas used, and most likely all the others, contained these organisms and that contamination did not occur by handling, etc. We realize that this is a startling statement to make yet we are forced to come to this conclusion. All our bacteriologic work was done carefully and all blood cultures were controlled by always planting sterile adult blood kept in the laboratory on the same medium as was used to culture placental blood. It certainly was not a laboratory contaminant, as it would have been obtained in other cultures. We cannot explain why we did not obtain *Bacillus fecalis* from the surface of the uncleansed placenta and cord. Most likely we would have obtained the organism if we had cultured more. It is surprising that this organism should always be present. In fact, some of the blood was cultured in another laboratory in the city, and also yielded the same organism. Samples of various preservatives were also cultured after autoclaving storage, etc., but were sterile.

Studies on the reactions of the preservatives alone and in combination with blood were also done.

TABLE I

	pH WITHOUT BLOOD	pH FRESH BLOOD AND PRESERVATIVE	pH BLOOD AND DEAD BACTERIA
Moscow preservative	7.4	8.5	8.9-9.0
Glucose-citrate	7.6	8.5	Bacteria could not be killed by storage
Sod. citrate 5%	7.5	8.4	8.8
Citrate-saline solution	7.5	8.4	9.0

It can be seen from our results that the pH certainly played no part as far as reactions were concerned. It can also be seen that the bacteria caused alkalinization of the blood, and just by the addition of the blood to the preservative the pH rose. The reaction of the blood, we do not believe had anything to do with the cause of reactions. The similarity between the reaction of the Moscow preservative, the sodium citrate solutions, and the glucose solutions eliminates that as a factor.

Studies were also made on fresh placental blood with certified pipettes and counting chambers. Sahli hemoglobinometers, calibrated by O_2 capacity so that 100 per cent represents 14.5 gm. of Hg, were also used. The average hemoglobin value was 122 per cent on 60 consecutive samples; R.B.C. averaged 5 M; hematocrit 48 per cent; mean corpuscular volume 1 cubic micra; mean corpuscular hemoglobin content was 34.0×10^{-12} gm. hemoglobin.

The various blood types were in order of frequency, 4, 2, 3, 1 (Moss). Our results in the main agree with those of Grodberg and Carey who found that in 50 cases the baby's blood type had not changed on discharge. We, in addition, had the mothers bring the babies back several weeks after discharge. In two instances, we found that the placental blood had been Type IV (Moss) checked microscopically and macroscopically, and on checking the babies' types four weeks after discharge, we found that they were Type II. On going back over our records, we found that the placental blood in these two cases would not cross match with any of the patients who were also of Group IV, but did so with the patients who were Group II. We gave this blood without reaction to patients who were of the latter group. In these two instances, the baby's type was not checked at all during their tenure in the hospital. We interpret these results as meaning that occasionally placental blood is not type specific. However, we feel this to be of no practical significance since any incompatibility would be discovered in the cross matching between donor and recipient.

SUMMARY

1. Hematologic studies on placental blood revealed that such blood would be desirable for adult transfusion if it could be collected sterilely, in sufficient quantities, and satisfactorily preserved.

2. An attempt was made to confirm the work of previous investigators who claimed placental blood could be adequately collected and preserved and subsequently given as transfusions to adults with a minimal number of reactions.

3. By using the usual bacteriologic culture media placental blood could apparently be collected and preserved sterilely, but the subsequent transfusion of these specimens was accompanied by a high percentage of reactions.

4. A comparative study of several different preservative solutions indicated that a 1.5 per cent sodium citrate in normal saline is the most desirable solution.

5. Further bacteriologic studies, using special culture media, revealed that a high percentage of the collected blood was actually contaminated. Several modifications of the method of collection did not eliminate such contamination.

6. Transfusion reactions could not be correlated with bacterial contamination or any other detectable factors such as amount of hemolysis, type of preservative, time of storage, etc.

CONCLUSIONS

Our studies indicate that the biologic significance of placental blood is somewhat greater than adult blood. Theoretically, the use of placental blood for transfusion is attractive; however, the technical difficulties encountered in its collection and sterile preservation are sufficient to make its use impracticable under the present state of our resources.

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214 North Potomac Street
Hagerstown, Md.

Veiga de Carvalho, H.: The Microscopic Picture of Syphilis of the Umbilical Cord and Its Significance in the Pathology of Gestation, Rev. de obstet. e ginec. de São Paulo **3:** 211, 1938.

In cases of syphilis the lesions found in the umbilical cord were endoarteritis, endophlebitis, infiltration with inflammatory cells, adventitial infiltration, necrosis and thrombosis of vessels.

There also were changes in the intima of the vessels, which were characteristic. The author makes a plea for the histologic examination of all umbilical cords of babies born of syphilitic mothers to establish the condition of the child.

Mario A. Castallo.

THE HISTOLOGIC EFFECT OF PROGESTERONE ON HYPERPLASTIC ENDOMETRIA

G. Emory Seegar, M.D., Baltimore, Md.

(From the Surgical Pathological Laboratory, Department of Surgery and the Department of Gynecology, Johns Hopkins Hospital and University)

THE present investigation was undertaken to determine whether physiologic changes could be produced in endometria showing abnormal patterns. For this purpose seven cases of endometrial hyperplasia were studied. The criteria for diagnosing hyperplasia were: (1) Straight, dilated glands showing reduplication and overgrowth of the glandular epithelium. (2) Absence of secretory changes in the epithelial cells and the presence of basilar placed nuclei and intact luminar membranes. (3) Density of the stroma which is characterized by small, tightly packed stromal cells with very little cytoplasm and by the infiltration of lymphoid cells.

MATERIAL

All seven cases in the present series were treated with synthetic progesterone* and endometrial biopsies were obtained before injection. A suction curette was used and in order not to destroy the existing endometrial pattern, thorough curettements were not performed. Treatment was usually begun during a bleeding phase. In the majority of cases, 50 mg. of progesterone were given in 5 mg. doses over a period of ten days as described by Browne. Endometrial biopsies were again obtained at the end of treatment. Three cases showed no microscopic effect. Four cases showed secretory changes in the endometrium. However, in no case could the microscopic picture be mistaken for a normal secretory pattern. A persisting irregularity of the glands gave evidence of the former pathologic state (Figs. 2 and 5).

In 5 cases of the present series estrogen and pregnanediol determinations were made on forty-eight-hour specimens of urine before and after progesterone injections. Pregnanediol determinations were performed by the Weil technique as described by Bucher and Geschichter.† No patient was excreting pregnanediol when injections were begun. The progesterone was recovered as pregnanediol in only two instances. It is significant that one patient, although given 20 mg. of progesterone daily, showed no secretory changes in the endometrium, yet the largest amount of pregnanediol was recovered in this case. The estrogen determinations showed normal values except in two instances.

RESULTS

In 6 patients a definite improvement in the bleeding symptoms was noticed. In 4 patients in whom injections were given over several months (Cases 2, 3, 5, and 7), fairly normal menses were established during treatment. However, since the condition is subject to spontaneous remissions and long periods of amenorrhea, an evaluation of progesterone therapy in cases of endometrial hyper-

*The progesterone used in the present studies was proluton furnished through the courtesy of the Schering Corporation.

†It has been found impossible to prevent hydrolysis of the pregnanediol sodium glucuronide to the free form under collecting facilities which must necessarily be used with dispensary cases. For this reason determinations based on the recovery of free pregnanediol were used.

plasia cannot be made on the basis of the limited number of cases in the present series. The impression is obtained that progesterone therapy may prove of value if doses are given in a manner which as nearly as possible reproduces the normal corpus luteum output of progesterone. The present studies indicate that 5 mg. of progesterone is probably the minimal dose which will produce anatomic changes. However, smaller doses may produce symptomatic relief.

CASE REPORTS

CASE 1.—The patient, C. G., was a 17-year-old, nulliparous colored girl who was first seen in the dispensary May 10, 1938, complaining of irregular menses. Her menarche had occurred at the age of 16 years and had never been established regularly. The duration of the flow was from one to two weeks with profuse

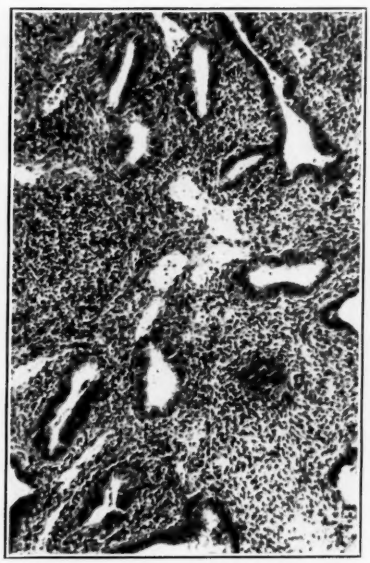

Fig. 1.

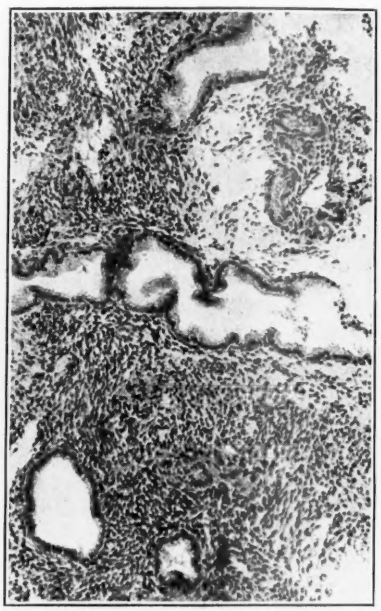

Fig. 2.

Fig. 1.—(Path. No. 47979.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone administered in 5 mg. daily doses. There is no evidence of secretory activity in these glands, which show marked reduplication of the nuclei of the glandular epithelium.

Fig. 2.—(Path. No. 47651.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone administered in 5 mg. daily doses. There is beginnin tortuosity of the glands, fraying of the cellular membrane at the luminar margin and a small amount of secretion in the lumen of the gland shown. The two cross sections of the glands show less activity, and one is slightly dilated, suggesting the previous hyperplastic pattern.

bleeding and no dysmenorrhea. Her present menstrual period had begun May 9 and the previous period had been from December 3 to 17. Physical examination revealed a very thin negress with normally developed puberal breasts, male hair distribution, slightly hypertrophied clitoris, and normal puberal pelvic organs.

As the patient was not bleeding profusely when first seen and her hemoglobin was 67 per cent, she was told to return before her next expected menstrual period for a suction curettage. She returned June 3 and an endometrial biopsy was taken at that time which showed endometrial hyperplasia. She failed to return for therapy and was next seen Jan. 17, 1939. At this time she gave a history of amenorrhea from May until October. Her October menstrual period lasted three weeks, and on January 2 she began to bleed again. This period was still

present at the time of her dispensary visit. A second curettage again showed hyperplasia and she was given a course of progesterone injections, 5 mg. daily for ten days. Her bleeding continued although less profusely through the administration of the hormone. A curettage January 28, following 50 mg. of progesterone, showed no microscopic change in the endometrium (Fig. 1). She ceased bleeding January 30 and, although she was instructed to return in two weeks for a second series of injections, she failed to keep her appointment. When next seen she gave a history of a normal menstrual period in February, March, and April. She began to bleed profusely April 26 and was still bleeding May 3 when a suction curettage again showed hyperplasia.

CASE 2.—H. D. was a 22-year-old housewife with two children, the youngest being one year old. Her menses had begun at the age of 12 years and during the first year she had bled for eight days every two weeks. She then established a twenty-six to thirty-day cycle and was regular, except for the two periods of pregnancy, until two months before her visit to the hospital. At that time she had a menstrual period lasting fourteen days. Her last menstrual period had lasted from June 27 to July 8 with profuse bleeding. On physical examination the patient was an obese woman with poorly developed breasts (the patient stated she had been unable to nurse her babies). The pelvis was normal except for a retroversion of the uterus which could easily be replaced. The basal metabolic rate was minus six. A suction biopsy showed endometrial hyperplasia. As the patient's hemoglobin was 95 per cent, no therapy was given and she was told to report for observation after her next menstruation. This period was also prolonged and profuse, lasting from July 21 to August 3. She began to bleed again August 22 and bled through September 6. Pregnanediol determinations for September 19 and 20 were negative. September 21 a suction curettage again showed hyperplasia and she was given 50 mg. of progesterone from September 21 to 30. She failed to report for a check curettage. Her bleeding recurred October 18 to 29. November 4 a curettage again showed hyperplasia and she received a second course of progesterone from November 4 to 14. During this time she noticed slight vaginal bleeding on November 13. Curettage November 14 showed an interval secretory type of endometrium (Fig. 2). November 16, two days after cessation of progesterone, she began to bleed and bled moderately until November 25. She had an apparently normal period December 15 to 23 and when last seen in August, 1939, she had had no recurrence of excessive bleeding.

CASE 3.—This patient was first seen May 2, 1935, at the age of 14 years. At that time she gave a history of profuse menses since the age of 12 years and constant bleeding for nine months. Her hemoglobin was 44 per cent. Therapeutic dilatation and curettage were performed and endometrial hyperplasia was diagnosed. She remained comparatively free from symptoms until November, 1938, when she began to bleed and continued until Feb. 23, 1939, at which time she returned to the dispensary for treatment. Physical examination revealed a thin negress of 18 years with the male type of hair distribution and a moderately enlarged clitoris. Pelvic examination was negative. Basal metabolic rate was minus two and her hemoglobin was 52 per cent. A suction curettage February 23 showed endometrial hyperplasia. A forty-eight-hour urine specimen showed no pregnanediol and 30 rat units of estrogen per twenty-four hours. Progesterone was begun February 28 and her bleeding ceased March 2. She had a recurrence of spotty bleeding March 6 to 9, when progesterone was discontinued and a curettage showed secretory changes in the endometrium (Fig. 3). March 11, two days following cessation of injections, the patient began to bleed and continued in an apparently normal period until March 17. She returned March 28 and a forty-eight-hour specimen again showed no pregnanediol, but 80 rat units of estrogen per 24 hours. From March 30 to April 6 she received 40 mg. of progesterone and suction curettage on April 6 again showed secretory changes in the endometrium (Fig. 4). A forty-eight-hour specimen of urine, collected over the last two days of progesterone administration, failed to demonstrate any pregnanediol. There were 12 rat units of estrogen per twenty-four hours. The patient bled moderately

from April 6 to 12. April 25 to 28 she received 20 mg. of progesterone and did not bleed until May 5 to 10. She had a normal period June 4 to 9 and has not returned for an examination.

CASE 4.—The patient was a 27-year-old negress who was first seen Feb. 13, 1939, complaining of constant vaginal bleeding since January 9. Her previous menstrual period had been from December 2 to 7. She had had five pregnancies, the youngest child being 4 years old. Physical examination showed a normally developed, obese negress with normal pelvic organs. Her basal metabolic rate was minus six.

Fig. 3.—(Path. No. 48200.) Low power photomicrograph of an endometrial biopsy taken after the first series of progesterone injections (50 mg.). This section shows beginning tortuosity of the glands, and secretory droplets in the glandular epithelium.

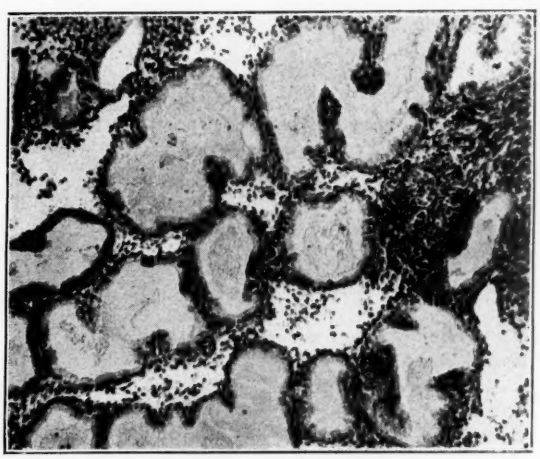

Fig. 4.—(Path. No. 48333.) Low power photomicrograph of an endometrial biopsy taken after the second series of progesterone injections (50 mg.). Here the endometrial glands show more marked tortuosity and evidence of secretion in the glandular epithelium than shown in Fig. 3.

Therapeutic dilatation and curettage were performed and the diagnosis of endometrial hyperplasia was made. She had no further bleeding until April 20, when she began to hemorrhage and continued until seen in the dispensary May 11. Suction curettage at this time again revealed endometrial hyperplasia. A forty-eight-hour specimen of urine showed no pregnanediol and less than 10 rat units of estrogen per twenty-four hours. Progesterone was given May 13 to 23, 5 mg. a day, and bleeding continued throughout. A curettage May 23 showed secretory endometrium

(Fig. 5). A second forty-eight-hour specimen collected over the last two days of progesterone injection showed no pregnanediol. The patient ceased bleeding May 27 and had no recurrence until August 4, when she bled again until curettage August 23. Endometrial hyperplasia was again diagnosed.

CASE 5.—F. A., a 12-year-old negress, was seen Feb. 28, 1939, complaining of profuse vaginal bleeding. Her menstrual period had begun December 18 and lasted until January 1. Her next period began January 18 and lasted until February 12 with profuse bleeding. Two days before the dispensary visit vaginal bleeding again recurred. Physical examination revealed a very well-developed child of 12 years with normal pelvic organs. Her basal metabolic rate was minus 13. A suction curettage showed an interval endometrium with a hyperplastic pattern. She received 5 mg. of progesterone daily from March 1 to 10 and a second biopsy showed a typical hyperplasia (Fig. 6). The patient ceased bleeding after the third injection. She had an apparently normal menstruation,

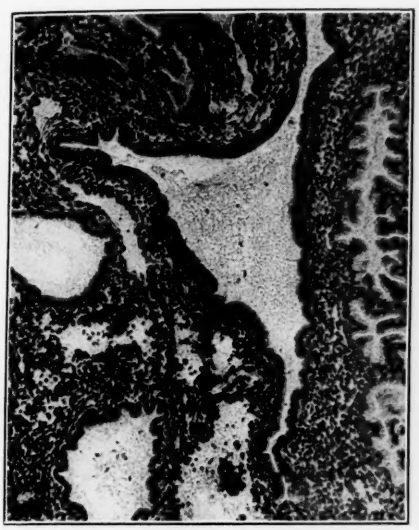

Fig. 5.

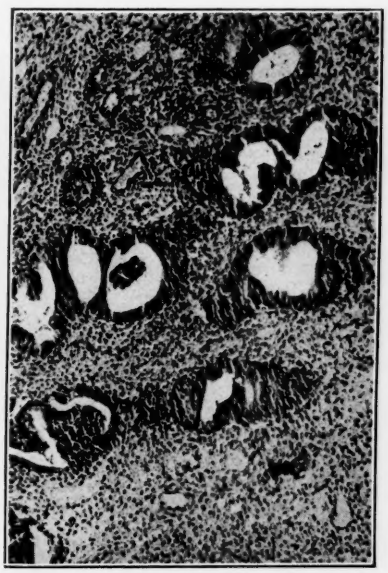

Fig. 6.

Fig. 5.—(Path. No. 48553.) Low power photomicrograph of an endometrial biopsy taken after the administration of 50 mg. of progesterone over a ten-day period. There is marked irregularity of the glandular pattern. The gland at the periphery shows marked secretory activity and tortuosity, while the two cross sections of glands show secretory activity of the glandular epithelium but remain dilated as in the previous hyperplastic pattern.

Fig. 6.—(Path. No. 48206.) Low power photomicrograph of an endometrial biopsy taken after 50 mg. of progesterone given in daily doses of 5 mg. There is no evidence of secretion in these glands, which show marked reduplication of the nuclei.

May 11 to 15, immediately following cessation of progesterone. Twenty milligrams of progesterone were given from March 20 to 23 and bleeding occurred from March 25 to 29. Twenty milligrams were again administered April 15 to 18 and bleeding occurred April 21 to 25 normally. When last seen in August, 1939, she had continued to have normal menses.

CASE 6.—This 26-year-old white woman was seen in December, 1937, complaining of constant, profuse vaginal bleeding. Her menses had begun at the age of 16 years and had occurred every twenty-eight days, lasting seven days until her first pregnancy in 1931. Following her delivery, she had amenorrhea for three years which was succeeded by profuse, irregular menses, lasting ten days. In October, 1936, a uterine curettage showed endometrial hyperplasia. She

remained well over a period of three months after which bleeding recurred. Her last menstrual period had begun in the middle of October and when seen she was still bleeding. The only significant fact in her past history was that she had had a thyroidectomy at the age of 19 years for a nodular goiter without hyperthyroidism. Physical and pelvic examinations were negative. Her hemoglobin was 41 per cent and her basal metabolic rate was minus twelve.

A forty-eight-hour urine specimen showed no pregnanediol. A suction endometrial biopsy November 14 showed endometrial hyperplasia. On November 18 she was given 50 mg. of progesterone in four injections over a period of eight hours and total urine specimens were collected November 18 and 19. Four and seven-tenths milligrams of pregnanediol were recovered and 4.7 mg. were also recovered in a specimen collected November 20 and 21. Beginning November 22, she received 20 mg. a day of progesterone and total urine collections were made. No pregnanediol was recovered until November 26 and 27 at which time 2.8 mg. of pregnanediol were determined. November 28 and 29, 2.4 mg. of pregnanediol were recovered. The patient continued to bleed throughout the course of injections. A hysterectomy and biopsy of the right ovary were performed on November 30. The uterine endometrium showed hyperplasia and no evidence of secretory activity (Fig. 7). There were numerous follicular cysts in the ovary.

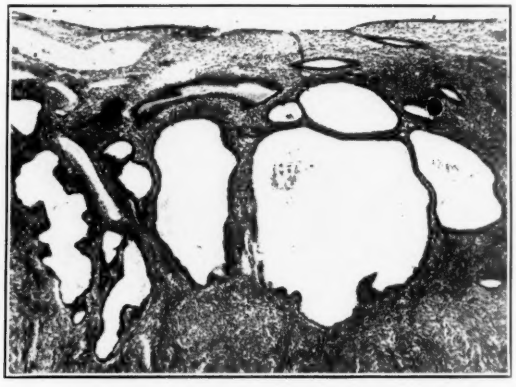

Fig. 7.—(Path. No. 59898.) Low power photomicrograph of uterine endometrium obtained by hysterectomy after administration of 210 mg. of progesterone. There is no evidence of secretory activity.

CASE 7.—The patient, E. W., was first seen in October, 1935, complaining of almost continuous vaginal bleeding for six years. Her menses had begun at the age of 13 years and had occurred every twenty-eight days, lasting five to seven days with no dysmenorrhea, until the age of 18 years, when her menses began to be prolonged. The condition had grown progressively worse until there were only five days during the month in which she was free from bleeding. On physical examination she was found to be a thin, underdeveloped individual with small breasts, showing hair about the areola and male hair distribution abdominally. The clitoris was unusually prominent, but otherwise the pelvic examination was negative. A therapeutic curettage was performed and the diagnosis of endometrial hyperplasia was made.

In August, 1937, she returned to the dispensary with the history of two months' amenorrhea following the curettage, and completely irregular, prolonged, profuse menses since. A forty-eight-hour specimen of urine showed no pregnanediol and an endometrial biopsy showed hyperplasia. She received 2 mg. of progesterone every other day from August 5 to 13, and bleeding which had ceased during the first two days of injections, returned from August 14 to 21. From September 8 to 20 she received 2.5 mg. of progesterone daily. Bleeding occurred September 17 to 21 and was less profuse. On October 7 an endometrial biopsy again showed

hyperplasia. Five milligrams of progesterone a day were given for six days and a specimen of urine taken over the last two days of administration demonstrated a trace of a crystalline substance which was assumed to be pregnanediol, but was too small an amount to verify with a melting point. A suction curettage at the end of treatment again showed hyperplasia. Three days after cessation of progesterone, the patient bled for eight days. On December 14, ten days before the next expected menstrual period, she again received 5 mg. of progesterone over a ten-day period. A curettage before therapy had again shown hyperplasia, but unfortunately after therapy an insufficient amount of tissue was obtained for a satisfactory microscopic study. Two days after discontinuation of progesterone the patient had an apparently normal five-day menstrual period. The same plan of treatment was carried out during the month of January; at this time an endometrial biopsy was obtained after 50 mg. of progesterone had been injected, which showed secretory changes. The patient again had an apparently normal menstrual period two days after her last injection was received. The following month the progesterone was reduced to 20 mg. in all and she again bled two days after withdrawal. No progesterone was given in March, and the patient had only scanty bleeding one day, March 23, and again on April 26. Menses lasted seven days and were profuse in June and July. She missed her August period and bled from September 24 to 30. On October 9 she again began to bleed and continued until November 28, when a biopsy showed a recurrence of endometrial hyperplasia. Forty-eight-hour urine specimens collected on November 12 and 13 and again November 19 and 20 showed no pregnanediol, and 30 and 14 rat units of estrogen per 24 hours, respectively. From November 28 to December 7 she received 5 mg. of progesterone daily. Bleeding stopped on November 30. A curettage on December 8 showed secretory changes in the endometrium, and a specimen collected on December 6 and 7 showed 0.7 mg. of pregnanediol with a melting point of 220° to 230°. There were 50 rat units of estrogen per 24 hours. Bleeding occurred from December 10 to 15. The subsequent course of treatment is recorded in Table I.

TABLE I

PROGESTERONE TREATMENT	BLEEDING DATE	ESTROGEN PER 24 HOURS	PREGNANEDIOL
—	—	116 Rat units	0—Dec. 26 and 27
50 mg. Dec. 28 to Jan. 7	Jan. 9-13	28 Rat units	0—Jan. 6 and 7
—	—	25 Rat units	0—Jan. 29 and 30
20 mg. Jan. 31 to Feb. 3	Feb. 5-10	16 Rat units	0—Feb. 2 and 3
—	—	—	0—Feb. 27 and 28 0—
20 mg. Feb. 28 to March 3	March 11-13	—	0—March 2 and 3
None	April 7-12	—	—
None	May 16	—	—

CONCLUSIONS

1. Endometrial hyperplasia may respond to progesterone and show changes resembling the physiologic response.

2. Three of seven cases of hyperplastic endometria did not respond to progesterone. Either 50 mg. of progesterone over a ten-day period is an insufficient dose or some cases are refractory to the hormonal influence.

3. In no case in the present series could a measurable amount of pregnanediol be recovered from the urine before treatment.

4. The amount of progesterone excreted in the urine as pregnanediol, when 50 mg. in 5 mg. doses is given daily, is insufficient to be recovered consistently in measurable quantities in cases of endometrial hyperplasia.

5. Progestational-like changes can be produced in the endometria of hyperplastic cases with doses of progesterone which are too small to be recovered in the urine as pregnanediol by present methods.

6. Progesterone can be recovered in the urine as pregnanediol even though progestational changes do not occur in the endometrium.

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THE USE OF THE NEUTRAL DIET AND HYDRATION IN THE TREATMENT OF TOXEMIAS OF PREGNANCY

RUSSELL R. DE ALVAREZ, B.S., M.D., ANN ARBOR, MICH.
(From the Department of Obstetrics and Gynecology, University of Michigan.)

THE care of toxemic patients has undergone considerable change during the past few decades. Impressed with the work of Newburgh on water balance, we have attempted to utilize his findings in the treatment of toxemias of pregnancy. In order to evaluate the results of our treatment, a study was made of the records of 435 toxemia patients admitted to the University Hospital between the years 1901 and 1938, inclusive. For purposes of comparison the records were divided into two groups, the first including the records of patients admitted between the years 1901 and July, 1931. The second group includes those admitted in the seven-year period from July, 1931 to July, 1938.

The average age for both groups studied is 23 years. The youngest patient was 13 years of age, the oldest, 46 years. The majority were between 20 and 25 years of age, corresponding to the general age group of pregnant individuals.

Primiparas constituted 63 per cent of the entire series. The average parity of the remaining 37 per cent was four. The largest number of pregnancies noted in any one individual was 12, the toxemia occurring first with the seventh child and increasing in severity with each succeeding pregnancy.

With the exception of four colored women, all the patients were white.

The nationality of the patients studied was about the same as a cross section of the population of the state of Michigan in general, mostly American. The remainder were German, Bulgarian, Hungarian, English, and Scandinavian. The latter were represented in extremely small numbers. It is interesting to note that only three patients were of Latin extraction.

The patients were classified according to Stander's classification of toxemias of pregnancy.[1] While we do not subscribe to this classification in its entirety, it is well known and widely used. The incidence of the various toxemias is shown in Table I. The so-called pre-eclamptic form predominated in both groups. Nephritic

TABLE I. COMPARISON OF PER CENT OF 2 GROUPS

TYPES	GROUP I (1901-31)		GROUP II (1931-38)		TOTAL	
	NO.	%	NO.	%	NO.	%
Low reserve	36	15.0	13	7	49	11.0
Nephritic	43	18.0	18	9	61	14.0
Pre-eclamptic	74	31.0	128	66	202	46.5
Eclamptic	35	14.5	20	10	55	12.5
Unclassified	53	22.0	15	8	68	15.5
Total	241	100.0	194	100	435	100.0

toxemia of pregnancy was second and eclampsia was third. These groupings were based on available clinical and laboratory data found in the patients' records. The relatively higher incidence of toxemias in Group II, from 1931 to 1938, was probably due to the development of more satisfactory investigative methods, and more complete recording of resulting data, and probably does not therefore represent an increase in incidence alone. There were 5,076 deliveries between 1901 and 1931, of which 241 were toxemic, an incidence of 4.7 per cent. In Group II there were 3,193 deliveries, of which 194 were toxic, an incidence of 6 per cent. This makes a total of 435 toxemias in 8,269 deliveries over the entire period studied, an incidence of 5.4 per cent for the entire period.

TREATMENT

For the patients in Group I, 1901 to 1931, treatment consisted in the main of: (1) general care with a short period of observation, (2) special measures, usually operative, for the termination of pregnancy. Most of the patients seen during this period were admitted in urgent need of treatment. Because of this, treatment usually resolved itself into a matter of determining the most satisfactory method of terminating pregnancy for that particular individual.

In keeping with the trend of the time, many of the patients seen during the period covered by Group I were, upon admittance, first placed on the then popular low-protein, salt-free diet. If this failed to control the toxemia symptoms, some means of terminating the pregnancy was carried out. The incidence of terminating pregnancy by cesarean section during the period covered by the first group was quite high and reached its peak, 11 per cent, in the years 1912 to 1916. As noted in Fig. 1, the incidence of cesarean section and induction of labor follow an inverse ratio.

That therapy in Group II was markedly conservative is shown by the reduced incidence of cesarean section, 2.6 per cent. Treatment during this second period was characterized by specific remedial measures, to be mentioned later, directed toward the control of the toxemia, and by induction of labor, usually by rupturing the membranes.

Therapy in Group II, 1931 to 1938, was first along the lines suggested by Arnold and Fay[2] and now commonly known as the Temple or dehydration method of treatment. Twelve patients were treated by this method, too small a number to warrant drawing any conclusion. One death occurred in the group treated by this method.

During the past six years, hydration has again dominated our medical management of these patients. In the presence of a significant toxemia, hospitalization, bed rest, sedation, neutral diet, ammonium chloride, and abundant fluids form the basis for our therapy.

One hundred and fifty-two patients in Group II were treated by this method. The neutral diet is the type suggested by Newburgh and Lashmet[3] consisting of foods which yield equal amounts of acid and basic ash to which are added foods which yield a neutral ash, such as butter, sugar, and tapioca. The diet is not strictly neutral, but somewhat on the acid side, a desirable feature in patients with edema. The diet is further characterized by its low sodium content and

a neutral or slightly acid ash. The food is prepared and served without salt. Bread is made without salt and sweet butter is used. The average diet contains between 70 and 85 gm. of protein.

Ammonium chloride is used to release the sodium ion from the tissues. It is given in gelatin capsules with the meals in doses from 8 to 12 gm. daily; when it is absorbed from the gastrointestinal tract, it is carried to the liver and there broken down to form urea. From there on, ammonium chloride is circulating in the blood stream in the form of urea and the chloride ion. The urea is excreted as such. The chloride ion, when it reaches the tissues, conjugates with the sodium from the sodium acid carbonate, NaH_2CO_3, and the sodium is excreted as sodium chloride. With the prolonged use of ammonium chloride, the kidney has a tendency to convert the urea back into ammonium ion, and consequently the ammonium is excreted as ammonium chloride, and the sodium ion continues to be retained by the tissues. For this reason, ammonium chloride is given for not longer than a period of three to four days at a time. With the elimination of sodium, edema fluid, which is retained by the sodium ion, is also given up. At the same time the intake of sodium is decreased by the neutral diet, which has a decreased amount of available base.

Fig. 1.

Fluids are forced, 4,000 to 5,000 c.c. being administered daily to insure a urinary output of from 2,500 to 3,000 c.c.

There are three advantages to this method of therapy: the free excretion of waste material and solids in water, the maintenance of normal water balance, and a decreased amount of available sodium. The neutral diet is also used in severe pre-eclamptic toxemias. Toxemic patients in coma are not fed for a period of three days to induce a mild acidosis. With this acidosis, diacetic acid produces the same effect as ammonium chloride in the other group by combining with the sodium ion and excreting it in the form of sodium diacetic acid. Fluids are given intravenously in large amounts to combat any element of uremia that may be present; we feel that the risk associated with forcing fluids is not very great, because the amount of rise in blood pressure is not of a significant degree. Also we do not feel that there is a risk of increasing cerebral edema if 5 per cent glucose solution is used, but do feel that there is a real risk of increasing intercellular fluids and retention of electrolytes if saline is used. If patients respond to this form of therapy, they are later placed on adequate neutral dietary intake, including ammonium chloride.

In considering the entire group of patients over both periods of study, it will be seen that the trend toward conservatism continues. Diet and fluid therapy are actively used to combat edema, which is thought to be a factor in the aggravation of toxemia.

MORTALITY

As noted in Fig. 2, the highest maternal mortality rate was coincident with the high rate of cesarean section. The evaluation of cesarean section as a means of terminating pregnancy or as a means of treatment on the basis of our data, is likely to be misleading. We have no desire to debate the question of cesarean section as a means of treatment for severe toxemia of pregnancy, but do wish to point out that the high mortality noted during the time when cesarean section was frequently used, 1912 to 1916, might, in part, be attributed to the undeveloped technique of the operation. In the first group, from 1901 to 1931, the maternal mortality rate for all patients was 7 per cent. The fetal mortality was 30 per cent. It is also to be noted that our fetal mortality rate reached its peak at the same time that the maternal mortality rate and the cesarean section rate were highest.

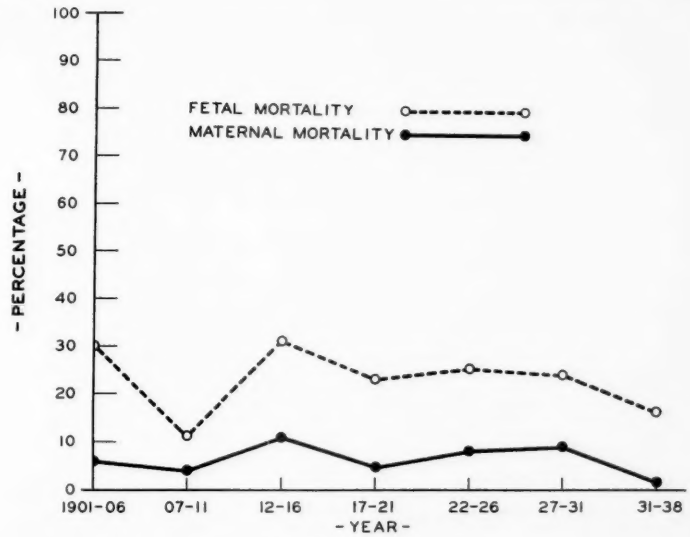

Fig. 2.

The maternal mortality rate for all Group II cases, 1931 to 1938, was 2.6 per cent, with a fetal death rate of 16.4 per cent. Of the maternal deaths in this period, four were directly the result of the toxemia, one occurring shortly after admittance in a patient having convulsions. One maternal death was the result of postoperative shock. Only one occurred in a patient who had been treated by the so-called hydration method, occurring ten hours post partum. The maternal mortality rate from toxemias of pregnancy in this clinic is lower at the present time than at any other time during the thirty-seven years covered by this study.

ECLAMPSIA

There were 55 cases of toxemia of pregnancy with convulsions. Of these, 28 patients were having convulsions at the time of admittance or developed convulsions within twenty-four hours. The remaining 27 developed eclampsia after having been in the hospital more than twenty-four hours.

The maternal and fetal mortality rates for both groups are recorded in Table II.

Cesarean section was resorted to in 13 of the 55 cases, but only one of these was performed during the last seven years.

TABLE II. MORTALITY, TOXEMIA WITH CONVULSIONS

	GROUP I (1901-31) 35 CASES		GROUP II (1931-38) 20 CASES		TOTAL (1901-38) 55 CASES	
	NO.	%	NO.	%	NO.	%
Maternal mortality	7	20	2	10	9	16
Fetal mortality	17	50	5	25	22	40

Twenty patients with eclampsia were treated during the past seven years, with a mortality rate of 10 per cent, or one-half that recorded for Group I casts. Of these, 16 patients were treated by neutral diet, hydration, and sedation only.

SUMMARY

1. Patients with toxemias of pregnancy admitted to the University Hospital are generally managed conservatively.

2. Toxemias of pregnancy are treated by what we call the hydration method, consisting of abundant fluids, neutral diet, ammonium chloride, bed rest, and mild sedation.

3. If, and when, this conservative regime fails to control the toxemia, termination of pregnancy by the most conservative means suited to the particular individual is carried out.

4. During the period 1931 to 1938, the maternal mortality rate has dropped to 2.6 per cent, the fetal mortality rate to 16.4 per cent, which is approximately one-half the death rate for patients treated during the years 1901 to 1931.

5. There has been one maternal death in the group of 152 toxemias of pregnancy treated by the hydration method since 1933.

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Boycott, Muriel, and Smiles, J. M.: Diagnosis of Hydatidiform Mole by Biological Assay, Lancet **1**: 1428, 1939.

The authors report a case in which hydatidiform mole was suspected and in which a 1 in 200 dilution of the urine gave a positive Friedman test. Subsequent evidence, including microscopic examination of the placenta, failed to confirm the diagnosis. They point out that the excretion of gonadotropic hormone in normal pregnancy may reach a higher level than is usually recognized. The maximal excretion occurs at about the stage of normal pregnancy (eight to twelve weeks) when the presence of hydatidiform mole is likely to be suspected. This excretion is increased in cases of pernicious vomiting. Although in most instances of hydatidiform mole and chorionepithelioma there is a larger excretion of gonadotropic hormone than in any other condition, there is such a range of excretion values that the diagnosis of hydatidiform mole on such assay alone is unreliable.

CARL P. HUBER.

ACUTE GONOCOCCAL PERIHEPATITIS

With Report of Five Cases

Walter M. Brunet, M.D., Chicago, Ill.

(From the Women's Division of the Public Health Institute.)

GONOCOCCAL perihepatitis as a pathologic entity was first accurately described by Curtis[1] in 1930. He reported the frequent occurrence of multiple bands of adhesions, which were defined as resembling "violin strings," between the anterior surface of the liver and the parietal peritoneum in female patients coming to operation who had a chronic gonococcal infection of the tubes.

In a later contribution Curtis[2] reported 24 patients upon whom he had operated and found these perihepatic adhesions, and all of them had a residual specific infection of the adnexa. These stringlike adhesions are found to extend over a wide area on the anterior surface of the liver and the anterior abdominal wall, but fortunately they are of sufficient length to permit free movement between the viscus and the muscular wall during respiration. Fitz-Hugh[3] in 1934 reported 3 cases of acute right upper abdominal pain associated with acute gonococcic salpingitis. One of his patients had a laparotomy during an attack, a presumptive diagnosis of acute cholecystitis being made. But when the abdomen was opened, an acute peritonitis was found involving "the anterior surface and edge of the liver and the abdominal wall." He crisply described the pathology in the following manner: "The peritoneum in these areas was injected and had the appearance of salt sprinkled on a moist surface." He further commented to the effect that "from the drainage tract in this case typical gram-negative intracellular diplococci were later recovered." The patient upon being told that gonococci were found in the wound admitted having a gonococcal infection with an accompanying salpingitis and bacteriemia some years previously. This internist and his surgical consultant reached the conclusion that what they had observed at the operation was the acute stage of gonococcal perihepatitis, the process described in its chronic form by Curtis.

Hinton[4] has reported his observations on adhesions in right upper abdominal pain, also Lyon[5] and Ellison[6] have discussed the causes of residual pathology in this region. Scott[7] has written on this subject and reported a case with a subdiaphragmatic abscess of gonococcic origin. Bearse[8] reported an interesting case in which the patient was operated upon for a presumable highly placed appendix during an acute attack, but examination of the abdominal organs revealed the presence of many cobweb and unorganized fresh adhesions between the liver and the anterior abdominal wall.

Recently Hertz[9] of the Mayo Foundation reported an interesting case of severe right upper quadrant pain which was suggestive of acute cholecystitis, but slides and cultures from the genitalia showed typical gonococci. A bilateral adnexitis was discovered. The patient received conservative treatment with hot baths, an erythema dose of x-ray and hyperpyrexia, and all symptoms were relieved, and she was rendered bacteria free promptly and returned to work one week after receiving fever therapy. This writer also discussed at length the clinical picture, pathology, differential diagnosis, and treatment of gonococcal perihepatitis.

In our clinic for women we discover and treat several hundred female patients presenting gonococcal infections annually. In the past

four years we have observed 5 cases in which a diagnosis of gonococcic perihepatitis was made. All of them had salpingitis following an acute gonococcal infection of the urethra or cervix or both. We found that tubal extensions are at times delayed as long as ninety days after the disease is contracted. The number of women who have a pelvic extension is large. In our clinic, considering all admissions,[10] upwards of 30 per cent have a tubal involvement.

CASE REPORTS

CASE 1.—(W-39512.) A white unmarried woman, aged 24 years, occupation: waitress, was admitted to the Institute Sept. 10, 1936, with a vaginal discharge and lower abdominal pain which had been present at intervals since receiving treatment for gonorrhea two years ago. She was accused of transmitting the infection ten days prior to our examination. She admitted being treated for gonorrhea two years ago and was discharged after a few weeks following one negative slide. She was exposed ten days prior to our examination.

General physical examination was negative. There was a profuse purulent discharge from the vagina. The urethra was inflamed and Skene's glands were thickened. There was no pain or tenderness on bimanual examination. Gonococci were found in the cervical slide. This was an acute infection. She received local treatment for several visits and a few days before her menses she complained of pain in the lower abdomen and thighs. Bimanual examination disclosed tenderness over the adnexa, but no masses were palpable. All local treatment was discontinued, and she was advised to stay in bed and use hot applications. On her visits to the clinic, intramuscular injections of foreign proteid at forty-eight- to ninety-six hour intervals were given. After receiving the fifth injection she complained of pain in the right upper quadrant on respiration, and she was tender on palpation. Auscultation was negative. The symptoms were suggestive of cholecystitis but quite atypical. Her temperature was 99° F. and it never went above 100°. Complete rest in bed and heat locally was the treatment which she had at home. Within four days she was free from pain and was out of bed within a week. The patient continued under our care following this complication, and she was pronounced bacteria free after three months' treatment. She was examined one year later and both tubes were found to be slightly thickened and the fundus was posterior and limited in motion.

CASE 2.—(W-46601.) A white, divorced woman, aged 20, occupation: waitress, was admitted to the Institute Feb. 18, 1939, with vaginal discharge, urgency, urinary frequency and painful urination, and pain in both lower quadrants. Her symptoms had been present for two weeks. She has also had metrorrhagia and rectal bleeding at intervals for several months. She has never received treatment for gonorrhea. She had an appendectomy and a right salpingectomy in 1934 and a left salpingectomy in 1937. She admitted numerous contacts while working in a tavern. The general physical survey showed no pertinent pathology. There was tenderness over the lower abdomen on palpation. The pelvic examination disclosed an eroded cervix, and there was a bloody purulent discharge in the fornix. A tender mass the size of an orange was found in the left adnexa. A rectal examination revealed large internal hemorrhoids. The slides from the urethra showed many typical intracellular diplococci. She was given foreign proteid in moderate size doses and 40 gr. each of sulfanilamide and soda bicarbonate, and advised to stay in bed and use any form of heat to her abdomen. She reported in four days and was still suffering pains in the lower abdomen. At this visit her temperature was 99° F. Her next visit was in forty-eight hours and she was greatly improved. The injections of foreign proteid were continued. The patient was out of the city for one week and upon her return she stated that after riding in a bus for ten hours she had an attack of pain in the right upper quadrant which was greatly increased upon deep inspiration and motion. The attack was sub-

siding when the patient next reported but she complained of tenderness on pressure over the liver area. Her temperature was normal at this time. We did not see the patient again for three weeks and at this visit, March 20, she was symptom free, but there was tenderness on palpation over the right costal margin. Local treatment was administered on April 5 and continued very irregularly for four weeks and at her visit on May 8 she was bacteria free. She failed to return for further observation. This patient had a mild attack of perihepatitis from which she rather promptly recovered.

CASE 3.—(W-39555.) A white married woman, aged 28 years, occupation: office clerk, was admitted to the Institute Sept. 15, 1936. Her complaints were vaginal irritation and discharge for five weeks. There was no history of any severe illness. She has been separated from her husband for eighteen months but admitted having sexual relations with him. The state of his health was unknown.

Examination disclosed an undernourished white female in poor physical condition. Teeth were carious, mouth foul, cervical and inguinal glands enlarged. The abdominal wall was relaxed and a small umbilical hernia was present. The vaginal examination disclosed an acute urethritis with profuse purulent vaginal discharge and an hypertrophy of the cervix which was lacerated and chronically inflamed. Fundus was anterior and normal. Adnexa were negative. Slides from the cervix showed many typical intracellular gonococci. Cervical slides were later found to be positive. The patient made good progress under treatment but at the first menstrual period, two weeks after admission, she had slight discomfort in the lower abdomen. The physical findings at this time were negative. For eight weeks her condition was satisfactory but at the third menstrual period, about twelve weeks after admission, she complained of severe pain in the lower abdomen without nausea or vomiting. Within forty-eight hours after the pain began in the lower abdomen, she reported to the clinic and complained of severe sharp pain on respiration in the right upper quadrant. Her temperature was normal. There was pain on deep palpation over the margin of the liver. Auscultation was negative. Hospitalization was advised but the patient refused as she could not afford the expense. She remained in bed at home and used hot applications to the right chest. She was comfortable while recumbent, and on her visits to the Institute, she received intramuscular injections of foreign proteids. She made a complete recovery and was symptom free within ten days. She was discharged from treatment and observation eight weeks after her acute attack. She was under observation for three months following the complication, and she was in excellent condition when last seen.

CASE 4.—(W-44615.) A white woman, single, aged 18 years, unemployed, was admitted to the Institute Aug. 8, 1938. She gave a history of an acute gonococcal infection twelve months ago and had received treatment until eight weeks before admission. She has had a persistent vaginal discharge for months, with irritation of the vulva, frequency and urgency of urination. She admitted sexual exposure one week before admission.

Our general examination was wholly negative. Vaginal examination disclosed a profuse purulent urethral and vaginal discharge. The uterus and adnexa were normal. The urethral and cervical discharge revealed many intracellular diplococci. A diagnosis of gonococcal urethritis and cervicitis was made and the patient placed on treatment. Her condition was excellent until her menstrual period which occurred four weeks after she was admitted. At her visit on September 8 she complained of pains throughout the lower abdomen. She was tender to palpation but there were no signs of rigidity. Bimanual examination disclosed tenderness over both adnexa, and the right tube was enlarged. There was no temperature or nausea or vomiting. The patient was receiving 40 gr. of sulfanilamide and soda bicarbonate daily. On her visits to the Institute foreign proteid was administered. With rest in bed and hot applications, the abdominal pain was relieved and she went back to work. At her second menstrual period, within eight weeks, she suffered two attacks of pain, but they subsided under conservative treatment. At her visit on Oct. 19, 1938, she complained of excruciating pain and tenderness over the right

upper abdomen. There was pain upon deep breathing and coughing. There was a slight elevation of temperature, 99.8° F. Examination of her chest was negative, but there was great pain on pressure over the costal margin. Hospitalization was advised and she consented and was admitted to the hospital. She remained in the hospital for five days and was improved, and against the advice of the attending physician she went home. Her condition remained stationary for several weeks, but at the end of the eighteenth week of treatment, she was in excellent condition. After her stormy and long-continued disability, she confessed to dancing, sexual excitement, and the use of alcohol. This patient was under treatment and observation for eight months. She was re-examined three months after being discharged, and there were no pelvic or hepatic residuals discoverable.

CASE 5.—(W-46555.) A white woman, single, aged 27 years, unemployed, was referred on Feb. 11, 1938, by her sexual partner who was under treatment for gonorrhea. She had noticed a vaginal discharge and pain and burning on urination for a week prior to admission. She had an uncomplicated gonococcal infection five years ago which was contracted from the same contact. There was no history of any confining illness or operations.

Our general physical survey was negative. Vaginal examination disclosed an acute urethritis, a profuse purulent vaginal discharge, and an erosion of the cervix. The right tube was slightly enlarged and tender. Slides from the urethra, cervix, and rectum all showed typical intracellular gonococci. She was placed on treatment, and topical applications were made to the urethra and cervix. Sulfanilamide and soda bicarbonate, 40 gr. daily, were prescribed. She returned within forty-eight hours complaining of pains in the lower abdomen, especially on the right side. Her menstrual period was not due for two weeks. At this visit her temperature was 99° F. and pulse 90, and the physical findings were negative. She was instructed to return home and stay in bed, and should her condition become worse she was to notify us. The patient left the city and her physician notified us that she was quite ill with severe pains in the right upper quadrant of the abdomen which resembled an "acute cholecystitis." He administered neoprontosil daily subcutaneously and gave her 60 gr. of prontosil by mouth every twenty-four hours and applied ice bags. The patient remained in bed for three weeks but her symptoms had disappeared after the first week's confinement. Local treatment was instituted after she was ambulant. She was dismissed as cured May 15, 1939, after being under treatment and observation for ten weeks. We made several physical examinations and a number of slides, and all of them were negative before she was dismissed from treatment.

DISCUSSION

There is no doubt that perihepatitis as a complication of pelvic inflammatory disease is much more common than the reported cases in the literature would lead physicians to believe. There can be little question that missed and wrong diagnoses of this condition are not uncommon, and especially is this true when a careful gynecologic examination and bacterial study of cervical and urethral secretions are omitted.

The question is often asked, "How does the infecting organism reach the liver?" We agree with the clinicians who have suggested that the gonococci reach the anterior surface of the liver by way of the lymphatics or blood stream. Pathologists have not yet reached satisfactory conclusions concerning the spread of the infection or which of these routes is the most common. Curtis has seen several cases where there has been an ascending infection along the colon, also inflammation ascending "the paravertebral gutter," and so perhaps some of these cases are ascribable to contiguity.

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159 NORTH DEARBORN STREET

DIAGNOSTIC FRIEDMAN TEST IN HYDATIDIFORM MOLE AND CHORIONEPITHELIOMA*

F. J. SCHOENECK, M.D., SYRACUSE, N. Y.

(From the Department of Obstetrics, College of Medicine, Syracuse University)

IT IS generally understood that the urine of patients with hydatidiform mole contains an excessive amount of the gonadotropic hormone, which is responsible for the reaction obtained in the Aschheim-Zondek and Friedman tests. With this thought in mind, we have attempted to determine the minimum amounts of urine, at the various stages of normal intrauterine pregnancies, which will give positive Friedman tests. The establishment of such normal standards provides the basis for a quantitative Friedman test.

We are expressing these standards in terms of actual amounts of urine required. Most quantitative hormonal studies report results in units per given amount of urine. However, the hormonal units do not seem to be generally agreed upon. In order to keep this quantitative test practical and avoid confusion, no attempt has been made to express results in units.

METHODS

We obtained our standards by intravenously injecting fractional amounts of urine in test animals of certain specifications. The animals used were virgin female rabbits, between the ages of 3.5 and 4.5 months and weighing at least 1,500 gm. The urine was injected in fractions as follows: 0.0125 ($\frac{1}{80}$) c.c.; 0.025 ($\frac{1}{40}$) c.c.; 0.05 ($\frac{1}{20}$) c.c.; 0.1 ($\frac{1}{10}$) c.c.; 0.5 ($\frac{1}{2}$) c.c..; 1.0 c.c.; 3.0 c.c.; and 5.0 c.c.

These standards, based on quantitative studies on 149 pregnant patients, are shown in the upper part of Table I. The lowest and highest dilution tests for the given weeks of pregnancy are tabulated. The average minimal amounts of urine necessary to produce positive tests are shown for the various weeks of pregnancy.

TECHNIQUE OF FRACTIONAL TEST

When a urine specimen is submitted from a suspected case of hydatidiform mole, a qualitative test is started, i.e., 15 c.c. of urine is injected in the marginal ear vein of a test rabbit in two doses of 7.5 c.c. each at intervals of twenty-four hours. The animal is laparotomized forty-eight hours after the first injection and the test read. At the same time the qualitative test is started, another animal is injected with 0.025 c.c. of the urine. If the qualitative test is negative, it is obvious that the fractional test will give no further information. However, if the clinical test

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is positive, the rabbit injected with 0.025 c.c. is opened. If this test is negative, further injections in smaller dilutions were made on additional test animals, i.e., 0.05 c.c.; 0.1 c.c., etc. On the other hand, if the 0.025 c.c. test is positive, higher dilutions are injected, i.e., 0.0125 c.c.; 0.00625 c.c., etc. We thus eventually get two fractional tests, one of which is positive and the other negative. The smallest fraction giving the positive reaction is considered the minimal positive test. Dilutions are made with tap water. Care must be taken that all test animals meet the requirements previously mentioned. Three or four animals are usually required for each quantitative test. Since we laparotomize the rabbits and use them in the future (an animal can be used on an average of four or five times), the test does not involve too much expense. Furthermore, any laboratory capable of performing clinical Friedman tests should be in a position to perform the fractional test.

HYDATIDIFORM MOLE

The fractional Friedman test findings in seven cases of hydatidiform mole are tabulated in Table I. It will be noted that in three of these cases (Mole 2, 4, and 7), positive tests were obtained with high dilutions, namely 0.00625 c.c., confirming the usual impression of a high concentration of gonadotropic hormone in the urine of these patients. Likewise in Mole 5, the positive test with 0.025 ($\frac{1}{40}$) c.c. is well above the standards of normal pregnancy for that particular period of pregnancy. However, study of the table will reveal that in Moles 1 and 6, more urine was required to produce a positive test, than the average for this stage of normal pregnancy, and in Mole 3, the contrast is not particularly striking, since the amount needed for this positive test was identical with the highest dilution test for normal pregnancy in that particular week.

Study reveals that those cases positive in high dilutions showed, on pathologic examination, a typical vesicular mole. In contrast Moles 1 and 3 were of the "fleshy" type and contained comparatively few vesicles. In Mole 6, the pathology was typical of the vesicular type, however, the specimen of urine was obtained the same day that the mole was expelled.

It is our impression that high dilution tests will be obtained only if one is dealing with an active vesicular type of mole. If the mole is of the fleshy type, or has, perhaps, ceased to grow, or is actually undergoing degeneration, we may not obtain positive reactions with high dilution tests.

CHORIONEPITHELIOMA

From a diagnostic viewpoint, the ordinary qualitative Friedman or Aschheim-Zondek test will suffice when chorionepithelioma is suspected. On the other hand, the quantitative test may be of value as a prognostic aid. We present the fractional Friedman tests on three patients with chorionepithelioma in the lower part of Table I. All of these cases terminated fatally.

It will be noted that two of these cases followed hydatidiform moles. This, of course, is generally understood, but it should serve to point out the necessity of carefully watching any patient who has had a hydatidiform mole. Such patients should have monthly Friedman or Aschheim-Zondek tests for at least one year after the expulsion of the mole. While it is true that these patients may have positive tests for a matter of weeks or possibly two months after the mole is expelled without actually having a chorionepithelioma, the positive test cannot be disregarded. Here the quantitative test will be of value. In the event of repeated positive qualitative tests, or positive high dilution tests, the patient is certainly entitled to a diagnostic curettage. It is generally conceded that a positive test is of diagnostic value in suspected chorionepithelioma and may be the first indication of such pathology.

DIFFERENTIAL DIAGNOSIS

We have found that other conditions associated with pregnancy may give high-dilution positive tests. While we have never obtained a positive test in normal uncomplicated pregnancy with amounts smaller than 0.05 ($\frac{1}{20}$) c.c., we have found that pregnancy complicated by hyperemesis gravidarum shows an excessive amount

TABLE I. FRACTIONAL FRIEDMAN TESTS (MINIMUM AMOUNTS) IN NORMAL PREGNANCY, HYDATIDIFORM MOLE, AND CHORIONEPITHELIOMA

	5 WK.	6 WK.	7 WK.	8 WK.	9 WK.	10 WK.	11 WK.	12 WK.	13 WK.	14 WK.	15 WK.	16 WK.	17 WK.	18 WK.	19 WK.	(PREGNANT)
Number of tests	6	15	15	13	21	16	22	12	5	6	6	3	2	3	4	
Lowest dilution (c.c.) Positive	5.0	5.0	1.0	0.5	0.5	1.0	3.0	3.0	1.0	3.0	1.0	3.0	0.5	1.0	1.0	
Highest dilution (c.c.) Positive	0.5	0.025	0.025	0.05	0.0125	0.025	0.025	0.025	0.05	0.5	0.1	0.5	0.1	0.1	0.5	
Average minimal amount (c.c.) Positive	1.66	0.915	0.286	0.235	0.423	0.237	0.421	0.563	0.51	1.07	0.45	1.33	0.3	0.53	0.625	
Mole 1										5.0						
Mole 2												0.0065				
Mole 3												0.5				
Mole 4											0.0065					
Mole 5															0.025	
Mole 6							0.5									
Mole 7								0.0065								
Chorionepithelioma 1	Positive with 5.0 c.c. Mole 10 months previous															
Chorionepithelioma 2	Positive with 0.025 c.c. Last pregnancy 3 years previous															
Chorionepithelioma 3	Positive with 0.025 c.c. Mole 4 months previous															

of gonadotropic substance in the urine. Five cases of hyperemesis were positive with 0.025 c.c. and two positive with 0.0125 c.c. All of these tests were confined to the interval between the seventh and twelfth weeks of pregnancy.

Likewise we have obtained high-dilution positive tests in multiple pregnancy. Thus, in two cases of twins studied, one was positive with 0.0125 c.c. and the other with 0.00625 c.c. A case of triplets was positive with 0.025 c.c.

With these findings in mind, it can be seen that care must be exercised in the interpretation of high-dilution positive tests. Thus, one could visualize a case of multiple pregnancy associated with hyperemesis gravidarum and complicated by a threatened abortion. Both clinical and laboratory findings might very well simulate hydatidiform mole. One sees the importance of the differential diagnosis, when we consider the contrasting treatments of these simulated possibilities.

SUMMARY

We have presented the technique of a fractional Friedman test, which can be carried out in any laboratory capable of performing clinical Friedman tests. The average minimal amounts of urine necessary to produce positive reactions in the various weeks of pregnancy are given. These findings form the basis of the quantitative Friedman tests.

Results of the quantitative tests of 7 cases of hydatidiform mole and 3 cases of chorionepithelioma are reported. While 4 of the patients with mole showed evidence of excessive gonadotropic hormone in the urine, the other 3 patients did not. Thus we may not rely entirely on this finding in all types of hydatidiform mole. Two patients with chorionepithelioma showed the gonadotropic hormone present in considerable concentration. It is felt that the ordinary qualitative test will suffice for diagnosis in chorionepithelioma, but that the quantitative test will often prove of value in this condition.

Since 2 of the 3 chorionepitheliomas developed consequent to the expulsion of hydatidiform moles, the necessity of following postmole cases with monthly Friedman tests for a period of at least one year is emphasized.

It is further pointed out that certain complications of pregnancy, namely hyperemesis gravidarum and multiple pregnancy, may also show an excess of the gonadotropic hormone in the urine. Hence, these conditions must be kept in mind in making differential diagnoses.

These findings of gonadotropic substance in the urine have been confirmed by quantitative studies on blood serum. These latter are not included, since it is felt that the urinary determinations will suffice for clinical application.

103 MEDICAL ARTS BUILDING

Kubota, T.: A Case of Fetal Death Due to Small Dose of Quinine, Jap. J. Obst. & Gynec. **22:** 128, 1939.

Quinine has long been used to stimulate uterine contractions. However, a few cases have been reported in the literature where quinine was responsible for the death of a baby. Kubota adds a case to this group. The total amount of quinine given to the mother was 0.29 Gm. (almost 4 gr.). The author believes that the baby died because it was sensitive to quinine. He urges caution in the use of this drug for the purpose of stimulating uterine pains at the end of pregnancy.

J. P. GREENHILL.

PARAMETRIAL ABSCESS AND PUERPERAL SEPTICEMIA DUE TO AN UNUSUAL ORGANISM*

MELVIN L. STONE, M.D., MED.SC.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division, Bellevue Hospital)

INFECTION with aerobic spore-forming motile bacilli has been reported in the literature but is sufficiently unusual to be interesting. The pathogenicity of many of the reported organisms has been limited to experimental animals, but Bais,[1] Charrin and De Nittis,[2] Kelemen,[3] Legros and Lecène,[4] Lindberg,[5] Senge,[6] Stregulina[7] and Sweany and Pinner[8] have reported various human infections with organisms of this group. Most of these authors described the organism as "pathogenic subtilis" and some used the term *Bacillus anthracoides.* In 1935 Siribaed[9] in Siam described a pathogenic variety of aerobic spore-forming bacillus, the origin of which he does not suggest, but which he called *Bacillus siamensis.* He believed it to be a pathogenic variety of *Bacillus subtilis.* Clark[10] in 1937 reviewed Siribaed's organism and compared it with other members of the group including *B. subtilis, B. cereus, B. megatherium, B. vulgatus, B. mesentericus, B. mycoides,* and *B. malabarensis.* As a result of this work he came to the conclusion that *B. siamensis* was identical with *B. cereus.* For identification Clark limited himself to morphology, cultural characteristics and pathogenicity for guinea pigs.

The following case, recently seen on the Obstetrical Service of Bellevue Hospital, is reported here because it illustrates infection with one of the aerobic spore-forming bacilli and because opportunity for thorough investigation of the responsible organism existed.

C. S., 19 years of age, white, was admitted to Bellevue Hospital on Dec. 30, 1938, at term with her first pregnancy. The patient had been observed in the prenatal clinic throughout the last six months of her pregnancy and, because of some question in the minds of several examiners as to the adequacy of her pelvis, stereoscopic x-rays had been taken. The results of a study of these plates indicated that the pelvis was small and gynecoid in architecture with slight android tendencies, and a fair midpelvis and outlet. Measurements in the precision stereoscope revealed a true conjugate of 10 cm., a transverse of the inlet of 11.5 cm., and an interspinous of 9 cm. The patient's Wassermann was negative and her course throughout pregnancy had been normal.

The patient sought admission because of the onset of lower abdominal cramps and backache eighteen hours before. These pains were not very strong. Examination at the time of admission revealed that the uterus was enlarged to the size of a term pregnancy and the weight of the fetus was estimated to be from 6½ to 7 pounds. The head was dipping into the pelvis in the R.O.A. position. Fetal heart sounds were of good quality. The blood pressure was 110/80, urine showed a trace of albumin, and red blood cells numbered 5 M with 96 per cent hemoglobin (Dare).

*This study was aided by a grant from The Commonwealth Fund.

The patient was admitted for observation, and on January 6, at 5 P.M., labor began with five- to seven-minute pains of fair duration. By 2 A.M. January 7, the cervix was 3 fingers dilated and the presenting part was at the level of the spines. Analgesia was obtained with sodium amytal and scopolamine, and at 6 A.M. the cervix was fully dilated. The presenting part was below the spines and the fetal heart was good. Two and one-half hours later, despite good pains, the patient still had not delivered. Vaginal examination revealed the head in the midpelvis in R.O.T. with considerable caput formation and molding. The cervix was completely dilated. Because of the prolonged second stage, abnormal position, and small midpelvis and outlet, Barton forceps were applied in the transverse and, after episiotomy and considerable traction, the patient was delivered of an apparently healthy male child, weighing 7 pounds 6½ ounces. The third stage required three minutes and no excessive bleeding occurred. The episiotomy was repaired and the patient was returned to bed in good condition.

On the first post-partum day, although the patient was comfortable, the temperature rose to 101° F. On the second day it rose to 102.2° F. and marked soft abdominal distention was noted. No tenderness was present. The patient had had no chill. Milk and molasses enema, Harris drip, and pitressin were effective in reducing the distention somewhat. A vaginal culture showed gram-negative bacilli. On the third post-partum day the temperature rose to 103.6° F., pulse to 130, distention again became marked, and inability to void was notable. The next day the temperature fell to 102° F. while the pulse remained at 140. During all this time the patient looked surprisingly well and offered no particular complaints. Lochia was not foul, distention persisted, urinalysis was negative, and the white blood count showed 17,000 cells with 74 per cent polymorphonuclear neutrophiles. It was believed that the patient was suffering from a syndrome closely resembling paralytic ileus and she was transferred to the isolation ward at this time. On the fifth post-partum day the temperature reached 104° F. and a blood culture was taken. This was reported later as showing staphylococci. The urine was normal. On the sixth and seventh days, the temperature continuing high, aerobic and anaerobic blood cultures were taken and, after incubation, gram-positive spore-forming bacilli were noted in pure culture in both media.

During the entire post-partum period, the patient had had only one slight chill. On the eighth day the temperature was 103.4° F. and complete examination was undertaken. The breasts were normal; the abdomen was slightly distended and soft. The uterus, at the level of the umbilicus, was firm and a little tender. The lochia was scant, brown, and not foul. Vaginal examination revealed the cervix to be soft and a finger tip dilated. The uterus was soft and not tender. No parametrial pathology could be made out. It was thought most likely at this time that the patient was suffering from a localized intrauterine infection. The red blood count was 4.3 M; Hg, 65 per cent; white blood count, 24,300 with 86 per cent polymorphonuclear neutrophiles. Stool cultures were negative for typhoid, paratyphoid A and B, and dysentery. On the ninth day a transfusion was started, but after 75 c.c. of blood had entered the vein, the patient complained of abdominal cramps and experienced a chill. The transfusion was discontinued immediately and 0.5 c.c. each of Magendies' solution and adrenalin was given. The temperature quickly rose to 106.4° F. There was no cyanosis and no respiratory distress. The pulse, however, rose to 150. After the intravenous administration of 2,000 c.c. of 5 per cent glucose in saline, the temperature began to fall and the reaction appeared to be over. Urinary output remained good and no hemoglobinuria was noted. On the tenth day, aerobic and anaerobic blood and uterine cultures were taken and in all a gram-positive, spore-forming bacillus was noted in pure culture. This organism was in all respects similar to that observed on the cultures taken on the sixth day. The temperature continued rising to 104° F. for the next three days, and on the thirteenth day a slow transfusion of 500 c.c. of citrated blood was given without apparent reaction. Urine culture taken at this time revealed *B. coli*, staphylococci and fusiform bacilli. On the fourteenth day, the temperature again rose precipitously to 104.2° F. and the patient complained of a sharp, stabbing pain in the right upper chest accompanied by a distressing nonproductive cough. Backache radiating to the groin was also noted. Examination revealed diminished

resonance over the right scapular region and diminished breath and voice sounds at the right apex anteriorly. The left lung was clear. The abdomen was slightly distended with moderate tenderness over the fundus uteri which was still palpable at the level of the umbilicus. In addition, there was some tenderness over the entire lower abdomen. Early pneumonia was suspected and the possibility of developing parametritis was also considered. The symptoms and temperature persisted throughout the next day and abdominal examination revealed a tender, fluctuant mass rising to the level of the umbilicus and extending five inches to each side of the midline. It was thought probable that what had been thought to be fundus was in reality the mass now interpreted to be cellulitis of the abdominal wall secondary to parametritis. The patient was given a third transfusion of 500 c.c. of whole blood without reaction. The following day she noted severe dysuria, and the urine specimen obtained that morning possessed a strong fecal odor and showed a thick foul-smelling sediment. This consisted of much amorphous and granular material and numerous clumps of pus cells. It was believed that the abscess of the parametrium had ruptured into the bladder. Further examination showed well-demarcated fluctuation in the lower abdominal wall up to the umbilicus. On pelvic examination, soft induration was noted in the fornices. The fundus, as such, could not be made out. A diagnosis of parametritis with dissecting abscess of the abdominal wall was made and incision and drainage was advised. Four grams of sulfanilamide daily was recommended because of the marked cystitis. Red blood count was 5.1 M; Hg, 65 per cent; white blood count, 20,850 with 90 per cent polymorphonuclear neutrophiles. Urine culture was again reported positive for *B. coli* and staphylococci. On incision of the parametrial abscess, 1,500 to 2,000 c.c. of foul, creamy yellow pus containing gas bubbles was evacuated. After drainage, the cavity was found to extend behind the space of Retzius and a cigarette drain was inserted into this area. The temperature on the next day dropped to 99° F. After irrigating the bladder with methylene blue, the abdominal dressings were stained with the dye, thus proving fistulous communication between the bladder and the abscess cavity. For the next two days the temperature remained at a level of 100° F. and aerobic and anaerobic blood cultures, repeated, revealed the continued presence of the same gram-positive spore-forming bacillus. The same organism in association with an anaerobic streptococcus was isolated from the pus evacuated from the abscess at operation.

Drainage continued from the abdominal wound but the temperature dropped to normal on the twenty-second post-partum day (fifth post-operative day). The drain was shortened gradually and bladder irrigations with 1 per cent methylene blue were utilized twice daily. Drainage diminished gradually, and the wound was irrigated with hydrogen peroxide by means of a small catheter. Definite clinical improvement now became manifest. On the thirteenth day postoperative, blood was drawn to test for precipitins and agglutinins against the organism which had been present. It was at this time that the temperature again rose to 104° F., accompanied by the onset of chills and right costovertebral flank tenderness. The clinical course, urinary findings, and lack of evidence of uterine infection made the diagnosis of pyelitis obvious; urine culture showed the presence of *B coli*. Despite sulfanilamide (3 gm. daily), signs and symptoms of pyelitis persisted for the next week and the temperature then gradually subsided so that five days later it was normal.

Cystoscopy performed before discharge revealed a small slit ½ cm. in length situated on the left lateral bladder wall. Pelvic examination was completely negative and the abdominal wound was well healed. The patient was discharged on the forty-ninth post-partum day, thirty-two days after operation.

DESCRIPTION OF THE ORGANISM

Morphology.—The organisms isolated in pure culture from the blood stream and uterus in the several cultures mentioned and found in association with an anaerobic streptococcus in the culture of the pus, were identical in all instances. They were straight or slightly curved

rods, measuring 3 to 5 micra in length by 1 micron in width. The ends, in contrast to the morphologic characteristics of the anthrax bacillus, were rounded. The bacilli, from liquid medium, were found singly, in pairs and in chains. In hanging drop preparations they were seen to be motile in a slow and stately manner. Flagella stains revealed that the organism possessed peritrichate flagellae, and spore stains showed large equatorial ellipsoidal spores. The organism possessed no capsule and was positive in its reaction to the Gram stain. With methylene blue, staining was uneven. The organism was aerobic and facultatively anaerobic.

Cultural Characteristics.—On agar plates, growth was exceedingly rapid, and, within five hours, definite colonial characteristics made their appearance. The colonies were large, spreading, raised, grayish white, dull and opaque. The surface was finely granular and exhibited a rhizoid appearance similar to that described for *Bacillus mycoides.* The colonies spread so rapidly that the advancing feathery, snow-crystal edge of one frequently overlapped an adjacent colony.

In meat infusion broth growth was likewise rapid with but slight turbidity. Growth at first seemed limited to the surface of the broth where a tough, leathery, grayish wrinkled membrane formed. Somewhat later the membrane sank to the bottom of the tube. On fresh horse blood agar, the colonies were slightly more regular. Slight hemolysis was noted after four days' growth and a distinct odor of ammonia was perceptible. The organism caused the liquefaction of gelatin in a stab culture.

Biochemical Reactions.—In liquid medium containing 1 per cent of the individual sugars, the organism fermented glucose, maltose, and sucrose with the production of acid but no gas, and failed to ferment inulin, salicin, lactose, and mannite. In litmus milk it caused decolorization and slow peptonization. Washed organisms in the presence of fresh glucose broth caused incomplete reduction of methylene blue in two hours. The supernatant fluid, however, caused complete reduction of methylene blue in thirty minutes, indicating the elaboration of a reducing agent by the organism. The negative methyl red test indicated that the final pH attained in 0.5 per cent dextrose broth after four days' incubation was more than 4.5. In 1 per cent peptone water the organisms were unable to produce indole. In common with other saprophytic organisms which break down proteins, this organism produced ammonia which was most distinctly perceptible on solid media. In addition, small amounts of H_2S were produced as determined by the lead acetate test.

The organism failed to reduce nitrates to nitrites, did not produce acetylmethyl carbinol, and did not produce catalase.

Experiments on Pathogenicity.—It is undoubtedly true that the organism isolated from the blood stream, uterus, and abdominal abscess was the cause of the pathologic process in our patient. Such being the case, experiments were undertaken to determine whether the organism was pathogenic for animals.

Pathogenicity for Mice.—The organism is pathogenic for mice. The intraperitoneal injection of 0.5 c.c. of twenty-four-hour culture and even the injection of similar amounts of old refrigerated culture, kills a 20 gm. mouse in two and one-half to six hours. This fact immediately raised the question as to whether the animals died from a preformed toxin or as the result of bacterial growth and true infection. In all cases of animals dead after inoculation, living organisms in pure culture were recovered from the site of inoculation, from the pleural cavity and from the heart's blood. The fact that death occurred so rapidly, however, led to the belief that a toxic effect might be of greater importance than the infection itself. Consequently, Berkefeld filtrates of twenty-four-hour cultures were made and mice were inoculated with 0.5 c.c. of the filtrate, shown by plating to be sterile. Such mice survived for four days while control mice, inoculated with whole culture, all died within six hours. In addition, a mouse inoculated with Berkefeld filtrate which had been heated to 80° C. for one hour survived. However, we realized that filtering through a Berkefeld and heating might adversely affect any toxin that might be present, and so the following experiment was performed:

A twenty-four-hour culture was divided into two parts. To one portion, formalin was added to a final concentration of 0.6 per cent. Both portions of the culture were then incubated at 37° C. for four hours and 0.5 c.c. of each was injected into mice. A similar quantity of 0.6 per cent formalin in sterile broth was injected into a third mouse as a control. Control platings, taken just before injection, revealed the formalinized culture to be sterile and the unformalinized culture to contain many colonies. While the mouse inoculated with the unformalinized culture died in six hours, the other animals survived.

A further experiment was run with centrifuged culture. Mice were injected with the supernatant fluid of an eighteen-hour culture, and despite the fact that this fluid was not sterile, the animals survived. In the case of a guinea pig which received 2.5 c.c. of the supernatant fluid, death occurred after eight days. All animals which received 0.5 c.c. doses of the washed and rewashed sediment of such an eighteen-hour culture died in two and one-half hours, and living organisms in pure culture were obtained from the peritoneal cavity, the pleural cavity and the heart's blood.

A mouse which had received supernatant fluid and which had survived was killed, and platings of the peritoneal washings revealed 200 colonies of the organism per c.c. Five-tenths cubic centimeter of this peritoneal washing was injected into a second animal which survived and from whose peritoneum no organisms could be secured. The experiment suggests that overwhelming numbers of the organisms are essential to produce death and that small numbers are easily removed, probably by means of phagocytic action. This observation is further borne out by the fact that repeated animal passage following the administration of sublethal doses of whole culture fails to cause death in animals subsequently inoculated with peritoneal washings of such mice.

The foregoing experiments suggested the determination of the minimum lethal dose. The following table indicates the results of such an experiment. All injections were made intraperitoneally.

TABLE I

AMOUNT 24-HOUR WHOLE CULTURE	RESULT
0.02	S
0.04	S
0.06	S
0.08	S
0.10	S
0.14	D within 12 hr.*
0.16	D within 12 hr.*
0.18	D within 6 hr.*
0.20	D 2½-5 hr.*
0.30	D 2½-3 hr.*
0.40	D 2½-3 hr.*
0.50	D 2½-3 hr.*

*The above represents the results of several experiments in each of which the killing time varied somewhat. Hence, range of such time is indicated in the case of animals dying as a result of inoculation.

While the great majority of mice inoculated with quantities of culture varying from 0.15 to 0.18 c.c. died, a few such animals survived. In all cases where amounts of 0.20 c.c. or over were given, all the animals died and organisms were recovered from the peritoneal cavity, pleural cavity and heart's blood.

It is interesting to describe the chain of events following injection and preceding death. About ten minutes after injection, definite hyperesthesia was present and the animals appeared irritable and excited. In a short time muscle spasm began to be apparent especially in the hind legs, which were extended convulsively, raising the animal. This effect gradually spread to the forelegs so that the abdomen was raised from the cage floor and parallel to it. Opisthotonos now became apparent, the animal appearing to stretch slowly, the back arching concavely, and the abdomen touching the cage floor. These convulsive seizures lasted about half an hour, after which the mouse became quiet and definitely hypesthetic. The hair became ruffled and the animals, appearing very ill, huddled together as though for warmth. They showed complete disinterest in food and died quietly without convulsions, and frequently maintained the same position they had assumed prior to death.

PRELIMINARY PROTECTION TESTS ON MICE

(a) *By Means of Sulfanilamide.*—It was first attempted to protect mice by means of sulfanilamide. Since previously it had been determined that therapeutically adequate doses of sulfanilamide (in the case of hemolytic streptococci), injected intracutaneously, killed the mice frequently, it was determined to delay absorption of the drug by means of suspending it in olive oil. The drug was carefully ground and suspended in olive oil so that 0.6 c.c. contained 10 mg. of sulfanilamide. The drug was administered in two blebs of 0.3 c.c. each into

the skin of the abdomen. Control animals treated in this manner survived. Mice given 10 mg. of sulfanilamide followed in two hours by 0.2 c.c. (1 minimum lethal dose) of whole twenty-four-hour culture intraperitoneally all died within six hours. It was thought that probably the concentration of sulfanilamide was not high enough to be effective, so that in a second experiment, mice were injected with 10 mg. of the drug daily for three days and on the third day, immediately after the third dose of sulfanilamide, were given 0.3 c.c. of whole twenty-four-hour culture intraperitoneally. These animals died within six hours, and living organisms were recovered in all cases. We realize that these experiments are inadequate to demonstrate the effect or lack of effect of sulfanilamide, for no analyses to determine concentration of the drug in the blood were undertaken. Likewise, there were no variations in the dose of the drug between the dose employed and the lethal dose of sulfanilamide.

(b) *By Means of Antibacterial Serum.*—Antibacterial serum was prepared by the injection of rabbits as follows:

Two hundred cubic centimeters of the twenty-four-hour broth culture of the organism were centrifuged and the sediment was resuspended in 5 c.c. of saline. This was heated to 60° C. for one hour, incubated at 37° C. for twenty-four hours to permit spores to germinate, and again heated to 60° C. for one hour. Tests for sterility revealed no living organisms. The suspension was left in the refrigerator and just before use was diluted 1:20 with saline. Rabbits received four series of five injections each, beginning with a series of 1 c.c. daily followed by a 2 c.c., a 4 c.c., and a 6 c.c. series with five-day intervals between each series. These series were followed by six daily intravenous injections (0.5, 2, 3, 5, 6, and 6 c.c., respectively, of living organisms) the virulence of which had been raised by mouse passage. Five days after the last injection the animal was bled from the heart and the serum collected.

Nine mice were divided into three groups. The first group received intraperitoneal injections of 0.3 c.c. of fresh twenty-four-hour culture plus 1 c.c. of normal rabbit serum. The second group received organisms plus antiserum in the same amounts, and the third group received a mixture of organisms and antiserum which had been allowed to incubate at 37° C. for one hour prior to injection. All mice in the last two groups survived while two of the three control mice died within eight hours. It seems, therefore, that there is definite protection afforded by antibacterial serum in the amounts used, although the test animals received only 1½ minimum lethal dose of the organisms.

Protection tests along similar lines with convalescent serum obtained from the patient on the twenty-fourth day of her illness failed completely to demonstrate any protective activity.

Serologic Tests.—Rabbit antiserum diluted 1:1 when mixed with HCl extracts of the organisms undiluted and diluted 1:4 and 1:16 gave positive precipitin reactions. Convalescent patient's serum failed to show the presence of agglutinins or precipitins against the organism.

DISCUSSION

Transfers of the organism isolated from this case were submitted to the American Type Culture Collection for identification. The opinion of Mr. N. R. Smith[11] was that the organism "agrees in all respects" with the *Bacillus cereus* cultures which he and Clark[10] described. On a cultural and morphologic basis there seems to be little doubt of the resemblance, although culturally it is difficult to distinguish *B. cereus* from *B. mycoides*. In an attempt to classify our organism more accurately, typical strains of *B. cereus* and *B. mycoides* were secured from the collection and both whole cultures and HCl extracts of the cultures were tested with serum prepared against the organisms we had isolated. The results are tabulated in Tables II and III.

TABLE II. AGGLUTINATION TESTS

CULTURE	PREPARED ANTISERUM*					
	UNDIL.	1:10	1:20	1:40	1:80	1:160
Patient's	+++	++++	++++	++++	++++	++++
Mycoides	+++	+++	+++	+	-	-
Cereus	-	-	-	-	-	-

*Made by inoculating rabbits with heat killed cultures of the organism obtained from the patient.

TABLE III. PRECIPITIN TESTS

	EXTRACTS								
	PATIENT'S			MYCOIDES			CEREUS		
	UNDIL.	1:4	1:16	UNDIL.	1:4	1:16	UNDIL.	1:4	1:16
Prepared antiserum	++++	++++	++++	-	-	-	-	-	-

From the above tables it is seen that cross agglutination occurs between antiserum prepared against the organism isolated from the patient and cultures of *B. mycoides*. No cross agglutination occurs with cultures of *B. cereus*. No cross precipitin tests were observed with either organism. How much significance should be placed on these findings it is difficult to say.

In tests for pathogenicity, using doses of 0.3 c.c. of twenty-four-hour culture, it was found that mice receiving cultures of *B. cereus* died in eight to ten hours. Mice injected with cultures of *B. mycoides* survived. It is worth noting that the growth of these two organisms was not nearly as profuse as the growth of the organism being investigated, and therefore comparable quantities of culture did not contain comparable numbers of organisms.

So far as the ultimate classification of this organism is concerned, we are still at a loss as to its proper place.

SUMMARY

1. A case of parametrial abscess and septicemia following childbirth is reported.

2. An organism, isolated repeatedly in pure culture from the blood stream and in mixed culture from the uterus and parametrial abscess,

is described as to: (a) Morphology and staining properties, (b) cultural characteristics, (c) biochemical reactions, (d) pathogenicity, and (e) serologic reactions.

3. This organism corresponds closely to the *B. cereus* described by Clark and also bears some resemblance to *B. mycoides* as far as many of its cultural, morphologic and serologic characteristics are concerned.

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239 Central Park West

ERYTHROBLASTOSIS FETALIS

A Report of Four Cases

J. Robert Willson, M.D., Ann Arbor, Mich.

(From the Department of Obstetrics and Gynecology, University of Michigan Medical School)

ERYTHROBLASTOSIS FETALIS is a disease of the newborn infant characterized by marked dysfunction of the hematopoietic and hemolytic systems, resulting in (1) failure of maturation of the erythrocytes or the overproduction of immature forms; (2) extrusion of abnormal numbers of immature erythrocytes into the circulating blood; and (3) abnormal destruction of erythrocytes. According to Diamond, Blackfan and Baty,[1] it may occur in three distinct forms: (1) congenital anemia of the newborn in which severe anemia is the most pronounced factor; (2) icterus gravis neonatorum in which the anemia is associated with the early onset of a marked icterus; and (3) congenital hydrops or universal edema of the fetus in which anasarca is the most outstanding sign.

Although each of the three types is a definite clinical entity, the group has certain features in common, namely: (1) A familial incidence most frequently noted in icterus gravis neonatorum and congenital hydrops; (2) hepatomegaly and splenomegaly; (3) severe anemia with large numbers of erythroblasts in the circulating blood; (4) extensive extramedullary centers of hematopoiesis, noted especially in the liver, spleen, kidneys, and adrenals; and (5) frequently edema and enlargement of the placenta.

The clinical course of each of the three forms is somewhat different. Congenital hydrops reaches its greatest severity in utero and often results in the premature delivery of a stillborn edematous fetus. The

typical case presents hydramnios, a large friable placenta, dark yellow amniotic fluid and golden yellow vernix.[2] Examination of the fetus reveals enlargement of the heart, liver, and spleen and extensive extramedullary hematopoietic centers. Hemosiderin may be present in the liver, but usually is not found in the spleen. Blood examination reveals a severe anemia with many immature cells of both the red and white series. In icterus gravis neonatorum, the most characteristic finding at birth is a marked pallor of the skin and mucous membranes which is soon followed by the development of increasing icterus. The placental changes may be identical with those of congenital hydrops. Except for the edema the findings on examination are identical with those of congenital hydrops.

Treatment in all types is directed toward stimulation of the bone marrow and decreasing the severity of the anemia until the hematopoietic tissues can function normally of their own accord. The most effective manner of accomplishing this end is the use of frequent small transfusions of citrated blood.

The prognosis in all these cases is grave. As has been stated above, infants with congenital hydrops are usually stillborn and if they are born alive death usually occurs within forty-eight hours. The prognosis in icterus gravis neonatorum and congenital anemia is poor even with intensive therapy.

A review of the literature by Diamond, Blackfan, and Baty[1] shows that congenital hydrops has been recognized for a great many years. Ballantyne[3] (1898) reported 70 cases taken from the world's literature since 1614. Schritte (1910) first described the hematopoietic disturbance in congenital hydrops. The first mention of the pathologic changes was made in a report by Buchan and Comrie[4] (1909), who noted erythroblastosis, hepatomegalia, splenomegalia, and areas of extramedullary hematopoiesis in several cases of icterus gravis neonatorum. Since then there have been several completely studied cases of all three types added to the literature, notably those of Hueper and Mullen,[5] Ferguson,[6] Plaut and Bullard,[7] and Wanstrom.[8]

Four cases of erythroblastosis fetalis are reported here; one icterus gravis neonatorum, two congenital hydrops (a stillborn infant and one who lived one hour), and an infant who died four hours after birth. The diagnosis on the last baby was made by pathologic examination. All the infants were delivered in the University of Michigan Maternity Hospital, three of them within a period of one month.

CASE 1.—The mother, aged 22 years, was a gravida v, para iv, the former pregnancies having terminated as full-term normal spontaneous deliveries of normal infants. In 1936 a diagnosis of congenital syphilis and interstitial keratitis was made in this hospital and she was treated with five intravenous injections of arsphenamine and five intramuscular injections of bismuth. Advice to continue treatment with her local physician was not heeded. Upon questioning she stated that all her babies had been "very yellow" soon after birth, but there had been no apparent morbidity. The family history was otherwise negative.

Antenatal History.—The mother had measles, diagnosed by her local doctor, about three weeks before delivery. She had noted that fetal movements had been feeble all through the pregnancy. There was no evidence of toxemia on admittance to the hospital, but she had received no antenatal care and was first seen in labor. The blood Kahn test on admittance was positive.

Clinical Course.—The labor was uncomplicated. It was noted that on rupture of the membranes about 500 c.c. of clear amniotic fluid were expelled. The placenta measured 14 by 18 cm. and appeared somewhat edematous to gross examination. Respirations were spontaneous and immediate, but extreme pallor of the skin and mucous membranes was noted at birth. About four hours after birth, jaundice was noted and the infant appeared lethargic and stuporous. The jaundice rapidly increased to an intense yellow.

Petechial hemorrhages over the face, abdomen, and extremities appeared on the fourth day. At that time the lower border of the spleen was found to reach the pelvic brim and the liver edge was 5 cm. below the right costal margin. There was a soft blowing systolic murmur over the whole precordium. The hemoglobin was 29 per cent (Sahli), red blood count 820,000 per c. mm., and white blood count 29,000 per c. mm. The blood smear showed a high percentage of immature cells of both the red and white series.

The baby was given 75 c.c. of citrated blood intravenously and 125 c.c. of Ringer's solution that day. A continuous intravenous injection of citrated blood, totaling 250 c.c., was given on the fifth day; on the sixth day 125 c.c. of citrated blood and 100 c.c. of Hartmann's combined lactate Ringer's solution were given, and it was noted at this time that the color of the infant was considerably improved. Eighty cubic centimeters of citrated blood, and 300 c.c. of Hartmann's solution were given on the seventh day, and universal edema was first noted following their administration, the baby having gained from 3,020 gm. to 3,707 gm. in four days. It was felt that the edema was not part of the disease as, when the intravenous fluids were discontinued, the edema disappeared. On the eleventh day, 90 c.c. and on the twelfth day 100 c.c. of citrated blood were given.

Following the institution of treatment, gradual improvement was noted in the condition of the patient, the jaundice became less marked and the infant more alert. One month after birth the spleen was 2 cm. below the left costal margin, the jaundice had disappeared, the evaporated milk formula was being taken eagerly, and there had occurred a weight gain of 214 gm. during the preceding ten days.

Laboratory Findings.—The Kahn test for syphilis was negative on the cord blood and on venous blood on the tenth and thirtieth days.

Urine on the tenth day was negative except for large amounts of bile and urobilinogen which was positive in a dilution of 1:500; on the thirtieth day there was only a trace of bile and the urobilinogen was positive in the undiluted specimen only.

The stools on the tenth and thirtieth days were normal, both specimens containing bile.

Blood examination on the twenty-first day showed: hemoglobin 94 per cent (Sahli), red blood count 5,020,000 c. mm., white blood count 12,000 c. mm., the smear showed immature leucocytes and erythrocytes.

The Duke bleeding time was five minutes and fifty-five seconds on the tenth day, and the capillary tube clotting time three minutes and fifteen seconds. Fragility test on the thirtieth day was normal, hemolysis of the erythrocytes beginning at 0.42 per cent and being complete at 0.3 per cent normal saline in the blood of the patient and a normal control.

Roentgen examination of the long bones on the thirtieth day was negative for any evidence of syphilitic involvement.

Comment.—A nonsyphilitic infant was born with clinical signs typical of erythroblastosis fetalis, the diagnosis being substantiated by laboratory studies. Complete recovery followed the intravenous injection of a total of 720 c.c. of citrated blood and 525 c.c. of other fluids over a period of eight days.

CASE 2.—The maternal grandmother of this infant had thirteen children, six of whom (the first, second, third, seventh, eleventh, and thirteenth) are living and well. Five pregnancies terminated in miscarriages early in their course. The remaining children were born alive at term. One died on the second and one on the third day of life, both with severe jaundice, but no other information could be obtained.

Of the living children, five have married and had children of their own. The first, a female, has had three pregnancies, all terminating in the normal spontaneous

delivery of normal children who are alive and well. The second, a female, has had six pregnancies which terminated as follows: (1) miscarriage at three months; (2) miscarriage at five or six months; (3) and (4) normal spontaneous deliveries of normal infants who are alive and well; (5) miscarriage at three months; and (6) a premature delivery at eight months, the infant living four days. The third, a male, is the father of four children, two of whom died of unknown causes at five months and two years, respectively; the remaining two children are alive and well. The fourth, a female, has had two pregnancies, both terminating in the normal spontaneous delivery of full-term infants who are alive and well. The fifth, the mother of the patient under discussion, has had four pregnancies which terminated as follows: (1) normal spontaneous delivery of a full-term infant who is alive and well; (2) normal spontaneous delivery of a full-term infant who died in twenty-four hours; (3) normal spontaneous delivery of an eight months' fetus in this hospital. This baby died on the third day with severe jaundice; bile was reported to be present in the cord blood sent to the laboratory for the cord Kahn test. An autopsy was not permitted and no other data are available. The fourth pregnancy terminated in the birth of the abnormal fetus under discussion.

Other family history is noncontributory.

Antenatal Course.—The mother, aged twenty-six years, was followed in this clinic during her pregnancy. The blood Kahn test was negative. Late in pregnancy she developed a mild toxemia with ankle edema, one-plus albuminuria and a blood pressure elevation to 150/90 mm. Hg. During the latter part of the prenatal period she complained of a constant dull aching pain in the lower right quadrant which was not easily relieved.

Clinical Course.—Contractions began spontaneously and the patient was delivered of an edematous fetus following a labor lasting four hours and thirty-five minutes; considerable difficulty was encountered in the extraction of the fetus, because the marked edema prevented normal extension of the head. During the delivery a cervical dislocation was produced as was demonstrated at the time of autopsy. There was one feeble respiratory gasp after the head had been delivered, but further attempts at respiration were not noted despite vigorous attempts at resuscitation. Examination of the fetus revealed marked edema with a tremendously distended abdomen, the eyes were swollen shut, and the ears were pushed out at right angles to the edematous scalp. The total length was 43.5 cm., the circumference of the chest 33 cm., and of the abdomen 38 cm.

Following the extraction of the infant an unusually large amount of yellowish green amniotic fluid was lost. The placenta measured 31 by 24 by 5 cm. and was very soft, pale, and friable. The cord Kahn test was negative. Microscopic examination of the placenta revealed slight fibrosis and increased cellularity of the chorionic stems without evidence of hematopoietic activity.

Autopsy.—The gross examination revealed the marked anasarca described above, but an average amount of edematous panniculus. No developmental anomalies were noted. There was a dislocation between the fourth and fifth cervical vertebras, with fresh blood around the cord from the foramen magnum to the level of the sixth dorsal segment. There was marked edema of the scalp, periosteum, and brain with increased subarachnoid fluid.

The thymus was small and appeared normal. The heart measured 4.5 by 3.5 by 2.2 cm. and weighed 50 gm. (normal 14 gm.); the pericardial fluid was normal in amount. Further examination of the heart revealed a patent foramen ovale and patent ductus arteriosus. The lungs appeared normal.

The panniculus over the abdomen measured 4 mm. In the abdominal cavity were 225 c.c. of thin yellow ascitic fluid. The spleen measured 6.5 by 3.4 by 1.5 cm. and weighed 18 gm. (normal 8 gm.); there were no lymphoid follicles noted. The gastrointestinal tract appeared normal. The liver measured 11 by 5.5 by 4 cm. and weighed 164 gm. (normal 127 gm.); to gross examination it appeared normal. There was edema of the wall of the gall bladder. The left and right kidneys weighed 11 and 10 gm., respectively and showed remains of fetal lobulations. The pelvic organs appeared normal.

The spinal cord showed congestion and edema of the meninges with immature blood cells in the blood vessels. The brain showed post-mortem change and active areas of hematopoiesis. The lungs showed fetal atelectasis without evidence of hematopoiesis. The trachea and larynx were negative except for marked edema. In the thymus there were noted hematopoietic centers scattered through the whole gland. The spleen was markedly congested and showed extensive hematopoiesis. There were areas of hematopoiesis in the serosa of the small intestine and petechial hemorrhages in the serosa and mucosa. There was also hematopoiesis in the serosa of the appendix and colon. The liver showed patchy increase in the stroma of the islands of Glisson with many immature cells of both the red and white series in the stroma and sinusoidal spaces. The adrenals also showed patchy foci of hematopoiesis with patchy cortical lipoidosis. Small hematopoietic foci were noted in the urinary bladder, and increased hematopoiesis was noted in the lymph nodes. Bone marrow from the ribs, sternum, and vertebral bodies showed many immature blood cells.

Comment.—A nonsyphilitic infant was born with congenital hydrops. The family history revealed three cases of early severe jaundice with death of the infants, many miscarriages, and several infants who died in the first few days of life. The diagnosis of erythroblastosis fetalis was confirmed by gross and microscopic examination of the fetus.

CASE 3.—*Family History:* The mother, aged 19 years, was a gravida iii, para ii. The two previous pregnancies had terminated in the normal spontaneous deliveries of normal full-term infants who are alive and well. There had been no unusual symptoms during the antenatal course; nausea and vomiting in both pregnancies had been confined to the first trimester. No significant family history was elicited.

Antenatal Course.—The mother was first seen in the antenatal clinic four days before going into labor. Nausea and vomiting had occurred daily throughout the entire pregnancy. No fetal movements had been felt in the last three weeks before admittance.

Clinical Course.—The patient was delivered of a 2,700 gm., grossly edematous fetus after a twenty-hour labor. Examination of the infant revealed a slow regular fetal heart, with a loud systolic murmur heard over the whole precordium. The liver was palpable in the right lower quadrant of the abdomen, but the spleen could not be felt. The baby did not breathe despite all measures of resuscitation, and after one hour the fetal heart stopped.

The placenta measured 18 by 19 cm. and was pale and edematous with indistinct sulci between the cotyledons. Microscopic examination revealed no evidence of hematopoietic activity.

Autopsy.—The gross examination revealed marked edema especially of the scalp. The brain tissue was very soft, but no other abnormalities were noted.

There were 30 c.c. of sanguineous fluid in each side of the thoracic cavity. The thymus was small and appeared normal. The heart measured 4 by 4.5 by 1.8 cm. and weighed 21.5 gm. Both the ductus arteriosus and the foramen ovale were patent. The lungs were partially atelectatic.

The panniculus over the abdomen was minimal in amount. Upon opening the abdominal cavity it was noted that the liver edge was 5.5 cm. below the right costal margin. In the abdominal cavity there were 100 c.c. of sanguineous fluid. The spleen measured 6 by 3.5 by 1.5 and weighed 18.5 gm. No lymphoid follicles could be made out. The liver measured 12 by 9 by 3.5 and weighed 185 gm. The remaining organs appeared normal.

The microscopic examination showed numerous immature blood cells of both the red and white series in the circulating blood with areas of hematopoiesis in the spleen, adrenals, kidneys, generative organs, lymph nodes, trachea, and bone marrow.

Comment.—An infant who lived one hour was born with erythroblastosis fetalis. The family history was noncontributory. The clinical diagnosis was confirmed by pathologic examination of the fetus.

CASE 4.—The mother, aged 42 years, was a gravida xii, para xi. The previous pregnancies had all terminated in the normal spontaneous deliveries of full-term in-

fants, 10 of whom are alive and well. The eighth baby died on the eleventh day of its life of an unknown cause. No other significant family history was obtained.

Antenatal Course.—The pregnancy was entirely uneventful. The patient was first seen in the antenatal clinic two weeks before delivery; during the rest of the antepartum course, no abnormalities developed.

Clinical Course.—The mother was delivered of an asphyxiated baby following a normal five-hour labor. The respirations were delayed about twenty minutes, but the heart remained of good quality. Despite vigorous treatment the respirations ceased four hours post partum.

The placenta measured 18 by 21 cm. and appeared normal. The cord Kahn test was negative.

Autopsy.—The gross examination revealed a cyanotic infant with a few small petechial hemorrhages in the upper half of the body. There were petechial hemorrhages in the brain and spinal cord.

Upon opening the chest, 20 c.c. of clear yellow fluid were found in the right and 15 c.c. of the same type of fluid in the left thorax. The thymus weighed 18 gm. and surrounded three-fourths of the circumference of the trachea, but there was no evidence of compression. The heart measured 4 by 4 by 2 cm. and weighed 18 gm. Both the foramen ovale and ductus arteriosus were patent. The lungs were partially atelectatic.

The abdomen contained no free fluid. The liver edge was found to be 4.5 cm. below the right costal margin and 6 cm. below the ensiform. The liver measured 13 by 7 by 4 cm. and weighed 154 gm. The spleen and other organs appeared normal.

The microscopic examination showed large areas of hematopoiesis in the lungs, thyroid, thymus, liver, lymph nodes, and cervix, with many immature blood cells of both the red and white series in the circulating blood.

Comment.—A nonsyphilitic infant died four hours after birth. Pathologic examination showed erythroblastosis fetalis.

DISCUSSION

Although erythroblastosis fetalis may be considered as a definite clinical entity, there are certain other conditions which may simulate the disease and which may be differentiated from it only by complete study of the patient.

Congenital syphilis may resemble the condition. Diamond, Blackfan, and Baty report the birth of a full-term infant with jaundice noted at delivery and mucous membrane pallor during the first week of life. Examination showed enlargement of the liver and spleen, ecchymoses and petechial hemorrhages of the skin, severe anemia and many immature erythrocytes, and leucocytes in the circulating blood. Blood tests for syphilis were positive, and roentgenograms of the long bone showed osteochondritis, suggestive of congenital syphilis. Post-mortem examination revealed changes typical of congenital syphilis, and spirochetes were demonstrated in the tissues.

Infection with sepsis may be followed by severe anemia with immature circulating blood cells and visible jaundice. In these cases there is a temperature elevation, diarrhea, vomiting, and the signs of infection appearing before the blood picture changes.

In hemorrhagic disease of the newborn infant, the anemia depends on the amount of blood lost. Icterus, hepatomegalia and splenomegalia are usually not present, nor is there a marked quantitative change in the blood picture.

Congenital malformation of the bile ducts may be differentiated by the presence of acholic stools, the absence of anemia and immature blood cells, and a later appearance of the jaundice.

Physiologic icterus usually appears on the third day of life and is absent at the end of a week. The jaundice is less severe, there is no change in the size of the liver or spleen and the blood picture is normal.

Because there are so many other conditions which may simulate erythroblastosis fetalis, it is imperative that a patient presenting an early onset of jaundice associated with hepatomegalia, splenomegalia, and a blood picture typical of the disease be completely studied to rule out other conditions which may produce these signs.

Transfusion of citrated blood should be instituted as soon as the condition is recognized and must be continued until the normal function of the bone marrow is established, if any improvement in the condition of the patient is to be expected.

SUMMARY

1. Four cases of erythroblastosis fetalis, two of congenital hydrops, one of icterus gravis neonatorum with recovery, and one in an infant who died four hours after birth are reported. Blood Kahn tests on all were negative.

2. An interesting family history of many miscarriages, early infant deaths, and the death of three infants with severe jaundice was obtained from the mother of one of the cases of congenital hydrops. The family history in the other cases was not conclusive.

3. Post-mortem examination of three of the cases revealed hepatomegalia, immature cells in the circulating blood, and extramedullary centers of hematopoiesis. Two of the infants had splenomegalia.

4. Following frequent small transfusions totaling 720 c.c. of citrated blood to the patient with icterus gravis neonatorum, the liver and spleen gradually decreased in size, the jaundice diminished, the anemia improved, and the patient was apparently quite fully recovered in thirty days.

5. Erythroblastosis fetalis may be suspected if the placenta is large, pale, and friable, and there is an increased amount of amniotic fluid which may or may not be yellow tinged.

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SUBCUTANEOUS IMPLANTATION OF COMPRESSED CRYSTALLINE THEELIN PELLETS IN THE TREATMENT OF MENOPAUSAL CASES*

Preliminary Report

Henry G. Bennett, Jr., M.D., Gerson Biskind, M.D., and Jerome Mark, M.D., Baltimore, Md.

(From the Departments of Gynecology and Pathology, The Johns Hopkins University and Hospital)

USUALLY, in the past, estrogenic preparations have been administered orally and by hypodermic or intramuscular injection. By these methods frequently repeated doses have been necessary, over rather long periods of time. With the hope of obtaining a more prolonged estrogenic effect, we have thought it worth while to investigate a new method of estrogen administration, whereby pellets of compressed crystalline estrogenic substances are implanted subcutaneously to be absorbed slowly over a long period of time. Such a method has been described by Parkes and Deansley[1] and found effective in obtaining prolonged hormonal stimulation in animals. Consequently we have treated twenty-one patients with menopausal symptoms by the subcutaneous implantation of estrogenic pellets. In an effort to evaluate this type of therapy, we have (1) observed the modification of subjective symptoms such as hot flushes; (2) determined in all cases the urinary level of estrogen before and after pellet implantation, in order to obtain some idea of the rate and duration of the absorption of estrogenic substance from the pellets; (3) determined the urinary level of follicle-stimulating hormone before and after treatment in order to estimate the effect exerted by the absorbed estrogen on hypophyseal activity; and (4) in ten cases, studied biopsies of the vaginal mucosa obtained before and after treatment in order to ascertain the physiologic potency of the absorbed estrogen on the genital tract epithelium.

TECHNIQUE

Pellets of pure crystalline estrogens have been made by direct compression of the crystals in drilled, machine ground, steel plates. The pellets used have been 1.83 mm. in diameter, 2.0 to 3.0 mm. in length, and 5.0 to 6.0 mg. in average weight. The estrogen pellets have been sterilized in a dry steam autoclave at 250° F. under 15 pounds of pressure for thirty minutes. Implantations in our patients have been made through a twelve gauge hollow needle fitted with a stylette. The pellets are loaded into the pointed end of the needle, and the needle passed through the skin after procaine infiltration. Pressure on the stylette as the needle is withdrawn deposits the pellets in the subcutaneous tissues. Sterile technique is, of course, observed throughout the implantation procedure.

Dosage.—We have given in a single implantation from 3 to 10 pellets with a total weight of 8.0 to 50.0 mg. Several patients have received two or more implantations. In all, 40 implantations of estrogenic pellets have been made in 21

*Supported by a Research Grant from Parke, Davis and Company.

patients. In 34 instances, pellets of theelin* have been used, and in 6 instances pellets of other estrogenic crystals.

MATERIAL

The 21 patients treated include 13 cases of physiologic menopause, 6 cases of operative castration, and 2 cases of radiation menopause. Seven of these patients had previously been treated with hypodermic injections of estrogens in oil, and 2 patients had received radiation of the hypophysis with only temporary relief of symptoms.

METHODS

Estrogen determinations have been made on twenty-four-hour specimens of fresh urine. The twenty-four-hour benzene extraction method, with preliminary acid hydrolysis, has been used.[2] Estrogenic activity of the olive oil extract has been determined by its effect on the vaginal smear of the mature castrate rat.

Determinations of follicle-stimulating hormone levels have been made on concentrated morning specimens of urine, extracted by the alcohol precipitation method.[3] The gonadotropic activity of the aqueous extract has been determined by the follicle-stimulating effect on the immature (eighteen- to twenty-day-old) rat ovary, as seen in serial sections.

Vaginal biopsies have been obtained by means of a special biopsy clamp, sectioned after formalin fixation, and stained with hematoxylin and eosin.

A total of 179 estrogen and follicle-stimulating hormone assays have been completed thus far on urine specimens from the twenty-one patients studied. A total of 31 vaginal biopsies from 10 patients have been studied.

RESULTS

1. *Effect on the Urinary Estrogen Level.*—In 19 of the 21 cases studied, no estrogen (or less than 2.0 R.U. per twenty-four-hour specimen, the threshold of the method used) was found in the urine before pellet implantation therapy was begun. In 2 cases 4.1 and 3.8 R.U., respectively, were found in twenty-four-hour specimens before treatment.

In all cases the urinary estrogen level became elevated following implantation of estrogen pellets. The average level reached after treatment has been between 8 and 10 rat units per twenty-four hours. This elevation has already continued in most cases for ten weeks or more. In one case the urinary estrogen is still elevated sixteen weeks after a single implantation of pellets. In another case in which 17.0 mg. of crystalline estrogen in 6 pellets were implanted, the estrogen level in the urine rose from less than 2.0 R.U. to more than 9.9 R.U. per twenty-four hours, and at a determination done fourteen and one-half weeks after implantation, this level was still maintained. In this case, an additional implantation of 23.2 mg. of theelin in 7 pellets was made at the end of fourteen and one-half weeks, and the urinary estrogen ten and one-half weeks later was 19.8 R.U. per twenty-four hours. So in this case, 30.2 mg. of theelin, given in two implantations, have already maintained the urinary estrogen level at a relatively high point for six months.

Estrogen apparently does not appear in the urine for several days following pellet implantation. In one case daily urinary estrogen determinations were done, and no estrogen was found until the fourth day after treatment with 27.2 mg. of theelin. In most cases the peak level of urinary estrogen excretion has not been reached before the fifth or sixth week following pellet implantation. Considerable variation in different patients has been encountered in the amounts of estrogen excreted in the urine after approximately equal doses of pellets. Since these levels are fairly constant in a given patient, it seems likely that this variation in excretion depends either on factors influencing absorption of the pellets or on some as yet unknown factors active in the process of estrogen metabolism.

2. *Effect on the Urinary Follicle-Stimulating Hormone Level.*—Of the 21 cases studied, 7 had a urinary follicle-stimulating hormone level above 100 rat units per liter before treatment, two had levels between 50 R.U. and 100 R.U. per liter, 6 between 25 R.U. and 50 R.U. per liter, and 6 below 25 R.U. per liter.

*Supplied by Parke, Davis and Company.

TABLE I. RECORD OF CASES*

CASE	AGE	TYPE OF MENOPAUSE	TOTAL WT. OF PELLETS IN MG.	TOTAL NO. OF PELLET IMPLANTATIONS	ESTRO. BEFORE TREATMENT. R.U.	ESTRO. AFTER TREATMENT. R.U.	F.S.H. BEFORE TREATMENT. R.U.	F.S.H. AFTER TREATMENT. R.U.	FLUSHES BEFORE TREATMENT. Q.D.	FLUSHES AFTER TREATMENT. Q.D.	TIME AFTER FIRST IMPLANTATION. WK.	TIME AFTER LAST IMPLANTATION. WK.
1†	48	Phys. No. 135079	44.1	2	0	6.6	0	0	15	0-4	10	7
2†	48	Phys. No. 165878	67.2	2	0	14.4	0	0	10-16	0-3	21	6.5
3†	50	Phys. No. 166020	65.8	2	0	9.9	25	0	20-30	0-5	13.5	8.5
4‡		Phys.	64.4	2	4.1	15.6	100	0	15-20	0-2	9	2
5†	48	Phys. No. 29821	40.2	2	0	19.8	100	0	3-4	None	25	10.5
6†	57	Phys. No. 147209	50.2	2	0	--	25	0	3-4	None	12.5	8.5
7†	52	Phys. No. 160865	42.5	1	0	5.8	0	0	6-8	2-3	3	--
8†	53	Phys. No. 166482	22.9	1	0	10.6	0	0	10-12	0-1	2	--
9†	44	Phys. No. K-17175	19.8	1	0	8.0	25	0	4-5	1	10	--
10†	42	Phys. No. 119266	22.2	1	0	7.7	100	0	3-4	None	10	--
11†	52	Phys. No. 155294	22.0	1	0	2.0	25	50	10-12	8-10	4.5	--
12†	44	Phys. No. 122378	19.8	1	0	--	25	0	5-6	None	4.5	--
13†	53	Phys. No. 166295	27.2	1	0	2.6	50	25	3-5	--	4.5	--
14†	46	Cast. No. 176205	84.6	5	0	4.0	100	50	20-30	0-4	37	12.5
15†	39	Cast. No. 74392	121.0	4	3.8	15.5	25	50	18-20	0-15	20	6.5
16†	24	Cast. No. 157410	35.8	2	0	4.8	100	100	10-15	1-2	8	3.5
17†	43	Cast. No. 101903	50.0	1	0	9.9	100	0	15-20	7-8	7.5	--
18†	31	Cast. No. 143429	22.0	1	0	5.0	0	25	3-5	2-3	8	--
19†	24	Cast. No. 155639	22.7	1	0	4.5	100	0	8-10	2-3	16	--
20†	31	X-ray No. 155994	42.1	2	0	4.3	25	0	8-10	2-6	17	7.5
21†	47	X-ray No. 111919	45.7	2	0	3.0	50	--	10-12	1-5	10.5	4

*The designation "0" under estrogen indicates less than 2.0 R. U. per twenty-four-hour specimen, and "0" under follicle-stimulating hormone (F. S. H.) indicates less than 25 R. U. per liter of morning urine, each being the lower threshhold, respectively, of the methods used. In three of these cases an additional implantation has been made, but the follow-up assays have not yet been completed, and so these three implantations are not included in this table.

†From Johns Hopkins Hospital.

‡From a private patient of Dr. H. S. Everett.

Following the implantations of estrogenic pellets, the urinary follicle-stimulating hormone level dropped below 25 R.U. per liter in 10 of the 15 patients who had an initial elevation above 25 R.U. per liter. In these cases follicle-stimulating hormone disappeared from the urine between the second and fourth week following treatment, and has remained absent as long as twenty-five weeks. These patients are still under observation, and the depression of the urinary follicle-stimulating hormone level has persisted to date.

In 5 cases the amounts of urinary follicle-stimulating hormone has continued to be excessive in spite of the fact that in 4 of these cases the urinary estrogen rose to levels comparable with other cases in which the follicle-stimulating hormone disappeared. In one case more than 50 R. U. of follicle-stimulating hormone per liter persisted in the urine eighteen weeks after the institution of pellet therapy, even though the urinary estrogen output was 15.5 R. U. in twenty-four hours at the same time. In another case, in which the urinary follicle-stimulating hormone was consistently below 25 R. U. per liter during two months of preliminary observations, the urinary follicle-stimulating hormone rose to 50 R. U. per liter within two weeks following the implantation of 22.0 mg. of theelin in six pellets. During the same period the urinary estrogen had risen from less than 2.0 R. U. to more than 6.6 R. U. per twenty-four hours.

3. *Effect on the Vaginal Mucosa.*—In 10 cases biopsies of the vagina were taken before treatment, and in every case the mucosa was atrophic with a thin layer of stratified squamous epithelium. Following pellet therapy the vaginal mucosa uniformly showed increased growth with thickening of the squamous layer and mitotic figures in the basal layers. In most cases this growth activity has become evident within the first two weeks after treatment though in one case the mucosa was still atrophic in three and one-half weeks, but became proliferative within four weeks after a second implantation of pellets and has continued so for eleven weeks. In another case vaginal biopsy still shows proliferative mucosa twenty-one and one-half weeks after the beginning of pellet therapy. These cases, also, are still being studied.

4. *Effect on Subjective Symptoms.*—All patients have reported improvement, but the degree and duration of relief of symptoms have been variable. Eighteen of 21 patients have considered themselves to be relatively symptom free for periods varying from two to fourteen and one-half weeks after a single treatment. In every case the return of symptoms has been gradual, and a second implantation has again allayed the symptoms. In 3 cases the symptoms were considered by the patients to be improved only. In one of these cases, however, the number of hot flushes has been reduced from 8 to 3 per day, and this relief has continued for sixteen weeks following treatment.

The correlation between subjective symptoms, urinary estrogen levels, urinary follicle-stimulating hormone levels, and condition of the vaginal mucosa, has not been entirely uniform. In general the patients who have reported the most marked and prolonged symptomatic relief, have also had the most marked increase in urinary estrogen level and have had less than 25 R.U. follicle-stimulating hormone per liter remaining in the urine. On the other hand, in some cases the symptoms have begun to recur when the urinary estrogen level was still at its peak, and when the vaginal mucosa was still proliferative. Patients whose urinary follicle-stimulating hormone level has remained above 25 R. U. per liter have had only brief or partial relief of symptoms.

Remarks on the Use of Subcutaneous Pellets.—We have done 40 subcutaneous implantations of estrogenic pellets in 21 patients, and in no instance has there been infection, inflammation, pain, tenderness, or other unpleasant reaction at the site of implantation. With pellet therapy we have encountered no instance of uterine bleeding such as is sometimes seen after large doses of estrogens in oil. In no case have there been any detectable breast changes following pellet implantation.

DISCUSSION

In this preliminary series of 21 cases we have been able, by means of a simple subcutaneous implantation of compressed pellets of crystalline

estrogens, to elevate the urinary estrogen level and to produce relief of menopausal symptoms for relatively long periods of time. We feel that the method is simple enough that it can easily be carried out as an office procedure. The duration of effective estrogen supply is long enough to recommend this method of estrogen administration over the oral and hypodermic injection methods in general use heretofore.

We recognize the limitations of the value of urinary hormone assays as an index of hormone metabolism, but feel that the definite and prolonged increase of urinary estrogens in our patients after treatment indicates at least that the estrogen is absorbed from the subcutaneous pellets, and that the disappearance of follicle-stimulating hormone from the urine in 10 of 15 cases suggests that this absorbed estrogen exerts a beneficial inhibiting influence on the hypophysis in postmenopausal cases. The estrogen as absorbed from the compressed subcutaneous pellets is an effective stimulus of growth in the vaginal mucosa. It seems then that estrogenic substances administered by this method lose none of the physiologic properties of estrogens administered in other forms, and that this method, therefore, can be advantageously employed in any case requiring prolonged estrogenic stimulation.

SUMMARY

1. A method of subcutaneous estrogenic pellet implantation is described.

2. A preliminary series of 21 menopausal cases, in which the patients were treated by this method, is reported.

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Démarez, R.: Immediate Treatment of Postoperative Phlebitis in Gynecologic Surgery by Infiltration of the Lumbar Sympathetics, Bull. Soc. d'obst. et de gynéc. **38**: 364, 1939.

The generally accepted view is that postoperative phlebitis is due to infection and that slowing of the blood stream and increase in the number of blood platelets cause the initial thrombosis. Most cases of phlebitis are treated by strict immobilization for six weeks to prevent emboli. In 1934 Lériche advanced the physiopathologic conception of phlebitis in which he maintains that the edema of phlebitis is not due to simple stasis but that the parietal venous changes irritate the perivenous sympathetic nerves, as a result of which there is reflex arteriocapillary vasoconstriction. Since there is a hyperirritability of the perivenous sympathetics, the thing to do is suppress it. Most of the vasomotor reflexes of the lower limbs pass through the ganglia of the lumbar sympathetic chain. Hence, blockage of this chain by anesthesia will successfully suppress disturbances due to spasms. On this basis infiltration of the lumbar sympathetic is excellent treatment for postoperative phlebitis. Démarez reports three cases of phlebitis treated by this means, and he is enthusiastic about this new advance in the therapy of phlebitis. When the infiltration is carried out early, pain disappears, the temperature drops, and edema either does not appear or is minimal.

J. P. GREENHILL.

THE TREATMENT OF ABNORMAL MENSTRUAL FUNCTION WITH ESTROGENIC AND GONADOTROPIC HORMONES*

ADOLPH JACOBY, M.D., AND MAURICE G. DERBRUCKE, M.D.,
NEW YORK, N. Y.

(From the Department of Gynecology, New York Post Graduate Medical School and Hospital, Columbia University)

THE following report is based on a clinical evaluation of the effectiveness of estrogenic and gonadotropic hormones in patients with menstrual derangements.

The estrogenic hormone used was an active oral preparation known as emmenin. The gonadotropic hormone used was anterior pituitary-like substance. These preparations are derived from the human placenta by differential solubility. The estrogenic hormone, emmenin, is standardized so that one teaspoonful contains 120 day-oral (Collip) units. The gonadotropic hormone, A.P.L. or anterior pituitary-like, is at present standardized at 500 Collip rat units per c.c. At the time of beginning this study, each c.c. contained 100 units.

THERAPY AND DOSAGE

As a rule, one teaspoonful of emmenin in a glass of water was given three times daily. The contents of the glass were not drained at once, but sipped over a period of hours, in the hope that the estrogenic hormone could be concentrated more or less constantly in the circulation. Both the stock bottle of emmenin and the diluted emmenin were kept in the refrigerator.

Treatment with anterior pituitary-like hormone included a period of twenty-eight days. A series of 18 intramuscular injections of 1 c.c. each was given, the first seven on consecutive days, and the next eleven on alternate days. Since the strength of the anterior pituitary-like hormone has been raised to 500 Collip rat units per c.c., we have administered ½ c.c., containing 250 Collip units, at each dose.

Ninety-eight patients were treated and followed for three or more years. They were divided into two major groups:

1. Estrogenic dysfunction (71 patients), included oligomenorrhea, amenorrhea, dysmenorrhea, and menopause.
2. Gonadotropic dysfunction (27 patients), included those in whom the primary complaint was menorrhagia and metrorrhagia.

ESTROGENIC DYSFUNCTION

Oligomenorrhea and Amenorrhea.—(23 cases.) The criteria for classification in this group are:

1. A woman in the childbearing age.
2. Scanty or no menstrual periods.
3. The presence of grossly normal uterus and adnexa.

Often associated with these factors were, in order of their frequency, headache, dull lower abdominal pain, dysmenorrhea, and nosebleeds. The ages of the 23 in this group ranged from 17 to 42 years. The duration of the amenorrhea was

*The emmenin and anterior pituitary-like hormone were supplied by Ayerst, McKenna and Harrison.

from 2 to 24 months. Those with oligomenorrhea had a scanty flow throughout the period, which usually lasted one day.

Fourteen of this group were treated with emmenin, 4 were supplemented with anterior pituitary-like hormone, while 5 others received anterior pituitary-like hormone only.

The 14 women treated with emmenin above improved symptomatically. Periodicity was re-established in those with an amenorrhea of four months or less, In 85.7 per cent of these patients the correction was permanent. One of these, with a four months' amenorrhea, became pregnant. Failure to menstruate was universal in those having amenorrhea of six or more months. One girl, with an amenorrhea of six months and almost nightly "convulsive" seizures, was reduced to one in two or three weeks, but menstruation did not appear.

In those treated for oligomenorrhea, the periods were lengthened from one to three days. The amount of bleeding, however, was but slightly increased.

There were 4 cases in which emmenin was complemented by anterior pituitary-like hormone.

CASE 1.—Patient, 38 years old, had an amenorrhea of twenty-four months. Her periods were regular up to six months after marriage. Thereafter the interval lengthened. She was placed on emmenin for one month. No change occurred objectively or subjectively. The medication was changed to anterior pituitary-like hormone. She developed a sense of well being and "felt fine," much more so than when on emmenin, but no menstrual molimen, menstruation, or menopausal symptoms appeared.

CASE 2.—Patient, 22 years old, had scanty periods, one day in duration, recurring about every 40 days, and associated with dysmenorrhea. She was placed on emmenin. One month later she menstruated one and one-half days and again four weeks later for only one day. The medication was changed to anterior pituitary-like hormone. Menstruation recurred every four weeks and lasted four days. Five months later she became pregnant.

CASE 3.—Patient, 39 years old, had an amenorrhea three months; headaches. After one week of emmenin she menstruated and the headaches ceased. When she discontinued the emmenin the periods would likewise stop. Five months later she was placed on anterior pituitary-like hormone. The interval between periods was increased to five weeks. Emmenin was given again.

CASE 4.—Patient, 25 years old, had an amenorrhea of seventeen months following a curettage. She was placed on emmenin and felt well but did not flow. She was given anterior pituitary-like hormone and she developed hot flushes, with dysmenorrheic pains associated with a monthly menstrual molimen, but no bleeding. All symptom complaints were controlled with emmenin.

Of the 5 who received anterior pituitary-like hormone only, 2 discontinued treatment. The other 3 showed definite improvement.

CASE 1.—Patient, 19 years old, had an amenorrhea for three months. She passed clots with her periods or had nosebleeds and headaches. She received an incomplete series of anterior pituitary-like hormone (14 c.c.). Headaches were aggravated; she developed visual disturbances, puffiness of face, and abdominal discomfort. With the discontinuance of this treatment all these symptom complaints disappeared. Surprisingly enough, normal menstruation was established.

CASE 2.—Patient, 21 years of age, had an amenorrhea for eight months. After 7 injections she showed a strong female sex hormone reaction and developed periodic menstrual molimen without bleeding.

CASE 3.—Patient, 23 years old, had an amenorrhea of four months. After 8 injections, monthly periodicity of a "good flow, best in months" was established and with the exception of a two-month interval, she has since menstruated regularly.

Comment.—Recent temporary loss of menstrual function is apparently chiefly due to deficiency of the estrogenic hormone. The oral administration of an active preparation of this hormone is effective in overcoming this deficiency, thereby restoring normal menstruation. In a minority of patients the anterior pituitary fails sufficiently to stimulate estrogenic function of the ovaries. In these patients, the administration of the anterior pituitary hormone alone or in conjunction with the estrogenic hormone is effective.

DYSMENORRHEA

There were 17 patients in whom premenstrual, menstrual, or postmenstrual pain was the dominant symptom complaint. Twelve of these were divided into two groups.

A. Those with a diminished menstrual blood loss received emmenin daily for one month, which was repeated if necessary.

B. Those with an increased menstrual blood loss were given a course of anterior pituitary-like hormone injections.

There was a third group in whom the hormones were alternated.

Six in Group A responded favorably but only one was permanently relieved. Likewise, all who received anterior pituitary-like hormone because of the associated menorrhagia were promptly improved. One of these patients became pregnant. As in the emmenin treated group, only one was permanently relieved of pain.

In two, the treatment was alternated between emmenin and anterior pituitary-like hormone. One of these did remarkably well on anterior pituitary-like hormone. The pain and amount of flow were definitely diminished and the associated nervousness and emotional disturbances lessened. The other did as well on anterior pituitary-like hormone as on emmenin. Both of these women required continued treatment for a long time to maintain painless periods. With cessation of treatment, the dysmenorrhea promptly returned.

For dysmenorrheic women with diminished flow, emmenin was satisfactory, although temporary; the longest period of relief without continuous treatment being two months. Those in whom the menstrual flow was increased responded favorably to anterior pituitary-like hormone. Unfortunately, in our hands permanent relief was not the rule. However, freedom from discomfort lasted for as long as six months.

Comment.—The hormonal disturbance associated with or causing dysmenorrhea is apparently not always of the same nature. The relief of the pain seems to depend upon supplying the deficient hormone. The results obtained are almost invariably of a temporary nature.

MENOPAUSE

Thirty-one women were treated with emmenin for symptoms ascribable to menopause. All had an amenorrhea of from two months to twelve years. Hot flushes, followed in order of their frequency by headache and dizziness, nervousness, emotional instability, and chilly sensations were the most prominent symptom complaints. Eleven had an artificially produced menopause. Twenty-five were followed from one to two years. These were divided into:

A. Induced Menopause (12)	
Hysterectomy with bilateral salpingo-oophorectomy	6
Hysterectomy with unilateral oophorectomy	3
Hysterectomy with retention of adnexa	1
Hysterectomy with radiation	1
Radiation	1
B. Spontaneous Menopause (13)	
Unilateral salpingo-oophorectomy	2

Artificial Menopause.—Of the 6 who had hysterectomy with bilateral salpingo-oophorectomy, 2 were made worse and 3 were definitely improved by emmenin. One of the latter developed periodic menstrual molimen. All with retained ovaries improved and remained so after two months' treatment. The patient treated with radium was finally relieved by emmenin.

Spontaneous Menopause.—Eleven of these 13 women were promptly relieved with emmenin. As little as three drams proved sufficient in one patient. In another, 49 years old, with an established amenorrhea and all the classical menopausal symptoms, the symptom complaints disappeared and her periods returned. On withdrawal of the hormone, the amenorrhea and all the associated menopausal symptoms reappeared. She was kept under observation for two years.

In two, all the symptom complaints were aggravated. One developed a choking sensation with precordial pains which disappeared with discontinuance of treatment.

Of the two with unilateral ovaries, one improved while on emmenin, while the other was aggravated.

Comment.—The menopause with its associated vegetative imbalance is a fertile field for the successful administration of the estrogenic hormone. However, it seems that a more favorable response can be obtained in the presence of ovarian tissue. Relief from the symptom complaints is prompt, usually lasts for long periods and can be maintained by subsequent occasional doses. The effectiveness of oral administration of an active estrogenic hormone preparation contributes much to the ease of maintaining these patients under treatment.

GONADOTROPIC DYSFUNCTION

All patients presenting menorrhagia and metrorrhagia as the chief complaints, and in whom the pelvis was free of any apparent inflammatory or organic change, were classified under this head. Lumbosacral backache, headache, and mastodynia were prominent among the associated symptom complaints.

Twenty-four of the 27 women in this group were followed from one to three years. All received anterior pituitary-like hormone, in divided doses of 1 c.c. (100 Collip day units) daily for seven consecutive days, and 1 c.c. on alternating days for 11 more injections. The entire course included twenty-eight days. Two of these women had emmenin as well.

The immediate reaction, that is, control of the amount of blood loss and amelioration of the symptoms, was favorable in 22 of the 25, or 88 per cent. There were two failures. One 28-year-old patient, who had had a left salpingectomy and a right cystectomy and myomectomy, had no relief after 28 c.c. (2,800 day units) of anterior pituitary-like hormone. A dilatation and curettage was done four months after treatment was started. Curettings showed an early premenstrual phase. The periods continued to be profuse and lasted eight days.

The other patient who was 32 years old, with a history of thirteen days of profuse bleeding in each of the previous seven months, responded to the first course of anterior pituitary-like hormone. The menstrual period was reduced to six days. After three months of further treatment she reverted to her former cycle.

As mentioned above, there were two who in addition to anterior pituitary-like hormone received emmenin. One, 23 years old, complaining of dizziness, headache, weakness, and hot flushes at times, had been staining daily for two years. She was placed on emmenin. There was prompt improvement. The intermenstrual bleeding stopped and all her symptom complaints were relieved. However, when the emmenin was discontinued the metrorrhagia, that is, the daily scanty spotting, returned. Again she was given emmenin. This time the bleeding became profuse. Anterior pituitary-like hormone therapy was promptly instituted. After 15 c.c. of one hundred day units each, the amount of bleeding was decreased and after three additional injections of 200 day units each, all bleeding ceased. Her subsequent periods were regular, of four days' duration and moderate in amount.

The second patient was 21 years old. She menstruated profusely every two months, each period lasting seven days, being accompanied by large clots. In addition to painful breasts and a basal metabolic rate of plus 5, she had a mild hypertrichosis. After 10 injections of 100 Collip day units each, the next three periods occurred monthly, without clots, moderate in amount, and lasted only four days. Thereafter she ceased menstruating. The estrogenic hormone, emmenin, was given. After two and one-half months of daily emmenin, hot flushes appeared.

Two other patients followed a somewhat similar course.

The first of these was 36 years old, with a history of menorrhagia and metrorrhagia with clots. In December, 1935, she was placed on anterior pituitary-like hormone. There was prompt improvement. The menorrhagia and metrorrhagia were replaced by regular, periodic menstrual periods, moderate in amount and without clots. This continued until September, 1936, or about nine months. At this time she was admitted to a state hospital for a mental disorder. Her periods ceased. The amenorrhea was still present one year later.

The last of this group was an unmarried girl, 26 years old, who came to us in May, 1935, complaining of severe menorrhagia and metrorrhagia, associated with weakness and headache. Basal metabolic rate was plus 6. After 32 c.c. of 100 Collip day units in each cubic centimeter had been administered in divided doses, bleeding was finally controlled in August, 1935. Thereafter menstruation recurred every three weeks, just a small amount for one day. This continued for nine months, until May, 1936, when she skipped one period and thereafter the flow gradually increased until the bleeding again became profuse. Additional anterior pituitary-like hormone had no effect. In March, 1937, or about 10 months later, we were informed that after a course of 10 to 12 x-ray treatments, all bleeding ceased. She then developed a psychosis with suicidal tendencies and had to be committed to a state institution.

In the rest of this group, a single course of anterior pituitary-like hormone therapy as outlined above, was sufficient to ameliorate all symptom complaints, such as profuse and prolonged menstruation, intermenstrual bleeding, headaches, dizziness, and breast pains.

Comment.—It appears that anterior pituitary-like hormone in proper dosage is effective in regulating irregular or profuse menstruation. In some patients this action may be carried too far and as a result, oligo- or amenorrhea may occur.

DISCUSSION AND SUMMARY

The type of menstrual dysfunction may clinically indicate the responsible hormonal deficiency. This can be used as a basis for therapy. In our series of cases the majority with deficient or absent menstrual bleeding responded favorably to the oral administration of an active and potent estrogenic hormone.

This was accomplished by supplying a stimulus lacking in these patients. That the estrogenic hormone was not always missing, is shown by those patients who responded to the administration of the gonadotropic hormone.

In those with excessive or irregular menstruation, good results were obtained by the use of the gonadotropic hormone. It is, however, necessary to be cautious in its administration, lest an overaction occur and a "hyperluteinization" be established.

The results in dysmenorrhea, using the indicated hormone, are almost invariably of a temporary nature.

The condition which responds most readily to hormonal therapy is that produced by a lack of estrogenic hormone resulting in menopausal symptoms. The response appears to be better in those who have some ovarian tissue.

151 West Seventy-Seventh Street
471 Park Avenue

INTESTINAL OBSTRUCTION AS SEQUEL TO THE WEBSTER-BALDY OPERATION FOR UTERINE RETROVERSION

CLARENCE I. OWEN, M.D., AND FRANK A. KELLY, M.D., DETROIT, MICH.
(From The Grace Hospital)

IT IS valuable at times to call attention to certain inherent dangers that may follow fairly simple operative procedures. One such danger exists in the performance of the Webster-Baldy operation for retroversion of the uterus. This operation was first described by Webster[6] in 1901 and later by Baldy[2] in 1903. In 1915 Webster[7] again wrote concerning his operation reviewing the technique, and for reasons not disclosed warned that the openings made in the broad ligament during the course of the operation should be closed carefully so that there would be no aperture remaining through which hernia could develop.

REVIEW OF LITERATURE

In 1920 Richardson[5] reported a case of intestinal obstruction following the Webster-Baldy operation which had been done two years previously. The patient was 42 years of age. A loop of ileum was found herniated through an aperture in the right broad ligament. The perforation of the broad ligament was external to the round ligament which also passed through the opening. There was no aperture in the left broad ligament. Richardson believed that the round ligament on the right side was drawn through the broad ligament which may have been thin and too far away from the body of the uterus and possibly that too large an opening may have been made. He thought that these factors would tend to make the round ligament cut through the broad ligament toward the body of the uterus and median line. This tendency, he felt, would be increased by a recurrence of the retroversion, thus an opening or a perforation of considerable size might form. He assumed that the operation was done correctly and that the opening made in the broad ligament at the time of operation was properly closed.

In 1929 Pemberton and Sager[4] reported a case in a female, aged 39 years, of intestinal obstruction twenty-four days after a Webster-Baldy suspension had been done. The edges of the openings which were made in the broad ligament had not been sutured, thus leaving an aperture through which a loop of small intestine two meters in length had passed. In the same report they described a case of a female, aged 36 years, who was operated for uterine fibroids upon whom a Webster-Baldy operation had been done twelve years previously. At the time that she was operated upon for her fibroids, there was a large opening in each broad ligament at the point where the round ligament perforated the broad ligament. These openings were large enough to admit two fingers. There was no intestine in either of the openings.

Arnold[1] in 1938 reported a case of intestinal obstruction nine years following a Webster-Baldy suspension operation of a female, aged 34 years. Two years following the suspension she was delivered of a full-term child. About nine months after the child was born she had the first attack which might be considered as being due to herniation through an opening in the broad ligament. Following this she had about two attacks a year until about nine years after her operation, at which time she had an attack of intestinal obstruction for which she was operated upon and a loop of intestine was found incarcerated in the aperture in the broad ligament.

Parkes and Karabin[3] in 1939 reported a case of intestinal obstruction following a Webster-Baldy suspension operation which had been done fifteen years previously. No mention was made whether any pregnancy had occurred in the interim. A footnote in the same article stated that one of the authors (J. E. K.) participated in another case of intestinal obstruction in which a Webster-Baldy operation had been done ten years previously. This patient had two full-term pregnancies in the interim.

CASE REPORT

The case herein reported was that of a patient, aged 44 years, who had an operation for suspension of the uterus nineteen years previously. Following the operation three full-term pregnancies occurred. As long as twelve years ago or seven years following the suspension operation she complained of pains and tenderness in the lower abdomen and was told by a doctor that there was a tumor in the rectum. A later examination revealed no tumor and her trouble disappeared.

She entered the hospital Nov. 4, 1938, complaining of gaseous distention, obstipation, nausea, and vomiting. She stated that she was well until October 24 when she began having abdominal pains and cramps which were later generalizing throughout the abdomen and becoming associated with nausea, vomiting, and abdominal distention. There were intervening periods which lasted from two to three hours in which the pain was much less severe.

On the first day of her illness she took some castor oil which caused a bowel movement. On November 1 there was a bowel movement following an enema. She stated that there was no blood in her stools on these occasions. There were no other bowel movements during her illness.

The vomiting was not related to intake of food and was not projectile. It was green in color. She was unable to take solid food following the onset. For two days she had hiccups which persisted and were troublesome.

On physical examination she was found to be acutely ill, entirely rational and cooperative. The only abnormalities of importance in the physical examination were found in the abdomen which was markedly distended and tympanitic. There was no rigidity and the only pain or tenderness elicited was on palpation of the left lower quadrant in which area a soft indefinite mass could be felt. There was noted an old healed lower abdominal surgical scar which was not tender. No fluid wave could be elicited.

At the time of admission the nonprotein nitrogen of the blood was 150 mg./100 c.c. The whole blood sodium chloride was 330 mg./100 c.c. The white blood count was 57,000; the differential contained 95 per cent polymorphonuclear cells of which 47 per cent were nonfilaments, 4 per cent lymphocytes and 1 per cent monocytes. She had a temperature of 98.4° F., a pulse of 108, and respirations of 20.

An operation was done by Dr. Frank A. Kelly soon after admission. Under spinal anesthesia, a low left rectus incision was made. Upon opening the peritoneum large distended intestines were found which were dark in color. On slight manipulation a large quantity of free pus flowed from the incision. Because of the condition of the patient, no further procedures were carried out and drainage was inserted. She died fourteen hours after the operation.

At post-mortem examination, the only findings of importance were in the abdomen. The omentum was seen to cover the viscera and was fastened by old dense adhesions in the lower left quadrant. On freeing the omentum from this area a loop of small bowel presented which was brownish red in color; accompanying this there were about 300 c.c. of foul-smelling thin yellow pus. On removal of the intestinal tract, there was found that about 45 cm. of ileum were herniated through an opening in the large left ligament, about 1 cm. inferior to the midtubal region, the hernia extending from before backward passing posteriorly through the broad ligament into the cul-de-sac. This segment of ileum was strangulated, dark purple in color and had an area of perforation from which fecal material was exuding. Surrounding this mass there was a semiwalled-off abscess from which pus exuded. Further examination of the intestinal tract revealed numerous adhesions about this area and no diverticula, ulcers, or tumors. There was no opening in the right broad ligament.

DISCUSSION

There are a number of reasons for which openings may be found in the broad ligament following Webster-Baldy operation. The first and most important would be the failure to close the aperture made at the time of the operation. This was thought to account for the case reported by Pemberton and Sager[4] and must have been present in Webster's mind as a potential source of danger when he wrote his second article. A second reason could be a recurrence of the retroversion accompanied by pulling on the round ligaments, causing them to separate from the area where they have been attached to the broad ligament. A third reason could be due to growth of the uterus by tumor or pregnancy which would cause undue tension on the round ligament, thus tending to tear the broad ligament at the site of the previous operation.

The case reported herein, the case of Parkes and Karabin, and the case of Arnold were known to have had one or more pregnancies between the time of suspension and the time of the intestinal obstruction. None of the cases that had obstruction were accompanied by tumors of the uterus. However, Pemberton and Sager described a case in which openings were found in both broad ligaments but without any herniation.

It would seem that the Webster-Baldy operation, although simple of technique and a safe operation in careful hands, even when properly done, is not without its dangers in subsequent years, especially if pregnancy supervenes or if a tumor of any size forms in the uterus.

SUMMARY AND CONCLUSION

Including the case herein reported there are reports of 6 cases of intestinal obstruction due to herniation through an aperture in the broad ligament, occurring from twenty-four days to nineteen years following a Webster-Baldy operation. There is one case in which apertures were present without herniation.

In cases of suspected intestinal obstruction where previous operation has been done, it would be well to inquire from the patient whether the operation was for suspension of the uterus, and, if so, this should be kept in mind by the surgeon in order to govern the technical approach.

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OVARIAN PREGNANCY

J. Clough Frudenfeld, M.D., Inglewood, Calif., and
A. N. Webb, M.D., Los Angeles, Calif.

PATIENT, white, housewife, aged 20 years, gravida 0, was first seen in October, 1938, because of the complaint of sterility. The patient had been using contraceptive methods until the previous four months. The physical and pelvic findings were essentially normal. No treatment was advised at this time. She was next seen in her home on the evening of March 19, 1939, complaining of lower abdominal pain which was more severe in the right lower quadrant.

Menses began at the age of 12 and occurred regularly every twenty-eight days, lasting three days without pain. She gave a history of the usual childhood diseases, good general health and no previous surgery. Her last normal menstrual period occurred on Jan. 8, 1939. Her next period was on February 5, and lasted five days but the flow was intermittent. On March 5, the menstruation consisted only of a pink vaginal discharge which has continued daily since that time.

On March 16, as she sat down, she felt a severe knifelike lower abdominal pain more severe on the right which persisted for one-half hour. Two days later she ate a large dinner, and the nausea and vomiting which followed were attributed to the unusual food she had eaten. The following morning she had some vague cramping pains in the right lower quadrant of the abdomen associated with general abdominal soreness and a mild diarrhea. That evening a severe, knifelike pain began in the lower abdomen, somewhat more severe on the right, and not radiating to the back or thigh. Examination at this time did not reveal any pallor. The pulse rate was 88; the blood pressure was 120 systolic and 80 diastolic. The heart and lungs were normal. The abdomen was not distended, but there were moderately severe tenderness over the lower abdomen and considerable muscle guarding. The uterus apparently was normal in size and position. The pelvic examination was unsatisfactory because of tenderness which seemed to be more marked in the right adnexal region where a small, extremely tender mass was felt and thought to be the right ovary. The diagnosis of an ovarian cyst or of a tubal pregnancy was considered and the patient was advised to remain in bed for further observation.

One hour later the husband reported by telephone that his wife had fainted. Her blood pressure was 100 systolic over 80 diastolic, pulse 100, and temperature 100° F., just before she was sent to the hospital. There was no shoulder pain.

A catheterized specimen of urine showed nothing unusual. The hemoglobin was 79 per cent Sahli (17 gm. in 100 c.c.), and the white blood cell count was 14,500 per c. mm. with 82 per cent polymorphonuclears. Under anesthesia, bimanual pelvic examination revealed a 4 or 5 cm. doughy mass in the right adnexal region. Bright red blood was obtained on cul-de-sac puncture.

Upon opening the peritoneum, approximately 500 c.c. of mixed fresh and old blood were found. The uterus was normal in size and position. Both tubes and the left ovary were carefully examined and found to be normal. One pole of the right ovary contained a yellow tumor mass, 3 cm. in diameter, bleeding freely around a blood clot about 5 cm. in diameter. This mass was interpreted as a bleeding corpus luteum. The left Fallopian tube was not in contact with any portion of the blood clot. A wedge-shaped incision was made in the ovary and the yellow body peeled from its bed. The cut surfaces of the ovary were closed with interrupted mattress sutures of fine catgut. A portion of the blood clot was separated from the corpus luteum during its removal.

The patient recovered uneventfully and was discharged from the hospital on the twelfth postoperative day.

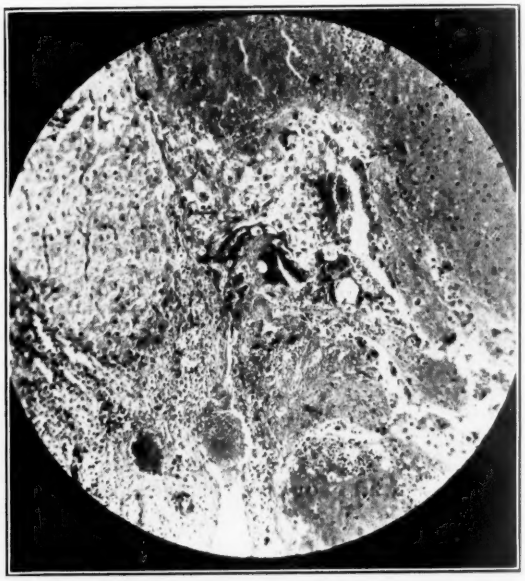

Fig. 1.—Microphotograph. (×100.) The pale zone on the left is composed of lutein cells. The dark areas on the right are blood clots. In the center a group of syncytial giant cells and Langhan's epithelial cells are seen. (Hematoxylin and eosin stain.)

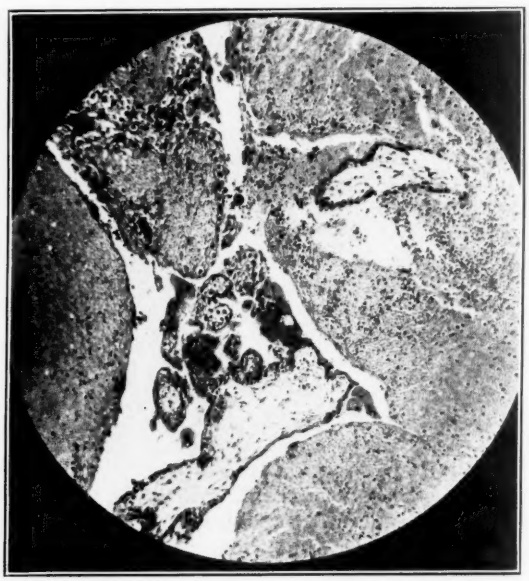

Fig. 2.—Microphotograph. (×100.) This is only one microscopic field removed from Fig. 1. Some of the clot is the same as that seen in Fig. 1. Note the chorionic villi, syncytial giant cells and Langhan's epithelium. (Hematoxylin and eosin stain.)

The following pathologic report is by E. M. Hall, M.D.

Gross Examination.—"The specimen consists of two separate pieces of tissue: (1) a hemorrhagic nodule of soft tissue which measures 2 by 2 by 1.5 cm. This has been opened and in the center there is a pale membranous cystlike structure, apparently the amniotic sac of an ectopic pregnancy. The embryo cannot be distinguished. The narrower irregular base of this mass matches exactly ringlike areas on piece No. 2; (2) a yellowish nodule, 2 cm. in diameter, oval in form, and slightly cystic in the center. Within the thin capsule there is a zone of bright yellow tissue about 3 mm. in thickness. The base is irregular where the mass (corpus luteum) has been removed from the ovary. On the smooth, rounded, outer surface there is a roughened circular hemorrhagic area where the first piece has been attached."

Microscopic Examination.—"Sections through (1) the hemorrhagic mass, show a broad zone composed of large, pale-staining lutein cells. There are many small, rounded, clear spaces in the cytoplasm of these cells where the lipoid has dissolved out.

"The main part of the section consists of a blood clot to which a portion of the corpus luteum is attached. Between the masses of clot are numerous chorionic villi, syncytial giant cells, and groups of Langhan's epithelial cells showing vacuolated cytoplasm (Figs. 1 and 2).

"Sections through (2) the corpus luteum, show a thin layer of ovarian tissue about the outside, forming a sort of capsule. The broad zone of lutein cells is 3 or 4 mm. in thickness. Unluteined granulosa cells are seen toward the outer border and also in the form of wedgelike masses extending for some depth into the luteinized zone. Red blood cells, fibrin, and partly organized clot are seen within the central cystic part."

Diagnosis.—"Ovarian pregnancy."

DISCUSSION

In this case as in the one reported by Thro,[4] chorionic villi were found embedded both in the corpus luteum and in the surrounding blood clot. The embryo was not found. Although we do not have microscopic sections of the Fallopian tubes to prove the absence of any pathologic changes, we feel justified in concluding that the findings are those of a primary ovarian pregnancy.

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Zelic, M.: Bleeding From a Pregnancy Corpus Luteum as an Indication for Laparotomy, Zentralbl. f. Gynäk. **62**: 989, 1938.

The literature in regard to ovulation bleeding, corpus luteum bleeding, and something of traumatic ovarian bleeding is briefly summarized. A case history is presented. A 23-year-old patient had had two normal pregnancies and three spontaneous abortions. The last menstrual period was seven days later than expected. After a forty-one-day period of amenorrhea, there was sudden pelvic pain, vomiting, and loss of consciousness. The patient was admitted with evidence of severe anemia and in shock. Operation showed 1,000 c.c. of blood in the peritoneal cavity. Bleeding was occurring from a corpus luteum in the left ovary which was removed. Careful examination of this showed no other abnormality than the source of the hemorrhage. Eight days later uterine bleeding began and an apparently normal three months' pregnancy was removed. The patient was discharged well.

The cause of the corpus luteum hemorrhage is ascribed to psychic disturbances.

J. L. McKelvey.

TREATMENT OF CERVICITIS DURING PREGNANCY*

ARTHUR G. KING, M.D., M.Sc., AND ROSELYN TOUFF, M.D.
CINCINNATI, OHIO
(From the Prenatal Clinic of the Cincinnati Health Department)

THE pregnant woman with a marked cervicitis and profuse leucorrhea presents a definite problem. Because of the generally increased sensitivity of the pregnant state she suffers with particular acuteness. Furthermore, although the correlation between cervicitis and puerperal infection has never been proved, it would seem theoretically that an infected cervix is a potential source of danger at the time of delivery. Yet, because of the gravid condition, there is a tendency to avoid any type of treatment.

Most of the textbooks specifically interdict any manipulation of the cervix during pregnancy because of the danger of inducing abortion or premature labor. This prohibition has extended in some clinics even to the insertion of a bivalve speculum. With the development of better technique, however, has come the feeling that the dangers are more theoretical than real, and within recent years, the amount of treatment permitted has gradually been increased.

Of the many methods of treating cervicitis in general, the actual cautery has proved among the most successful. It is undoubtedly more drastic than topical applications or caustic chemicals, but is, in careful hands and with due regard to conditions, perfectly safe.

A survey of the literature reveals the warning in almost every paper dealing with cauterization of the cervix that pregnancy is a contraindication, but none of the authors reports any data to support the statement. On the other hand, in 1931 Miller, Martinez, and Hodgdon[1] reported a series of 2,000 women in whom the cervix was cauterized antenatally. There was only one abortion, a percentage far lower than seen ordinarily in 2,000 pregnancies. Castallo and Montgomery[2] in 1935 stated that the cervix may be treated antenatally without danger to the mother or the embryo. In Goldblatt's[3] series of conization of the cervix, there happened to be 20 women pregnant from one to nine months, not one of whom went into premature labor or aborted. The evidence, therefore, seems to indicate that the dangers of treating the gravid cervix, even by so formidable a method as cauterization, are larely exaggerated.

The experiment reported here was undertaken in an effort to treat leucorrhea, due to nongonorrheal cervicitis, in pregnant women. The criteria for treatment were complaints of leucorrhea and the finding of either erosion or an old laceration or both. Gonorrheal cases were not treated. The cases were otherwise unselected and the data concerning the delivery were obtained from independent observers at the hospital. The treatment was given at one sitting, between the twentieth and thirtieth weeks of pregnancy, and consisted of fairly deep linear cauterizations on both lips of the cervix in more or less radial fashion, but including the lateral margins of the os where laceration was present. No

*Read at a meeting of the Cincinnati Obstetrical Society, December 21, 1939.

anesthesia was needed. Bleeding from a pulpy cervix occurred in a few cases but did not occasion alarm and did not persist longer than a day.

RESULTS

Including 2 cases from private practice, 48 women were treated, 13 primiparas and 35 multiparas. The records of 140 women seen concurrently in the same clinic were used for controls. Of the 48 treated patients, 2 moved away from the city and could not be located, but it is known that they were still pregnant two weeks after the treatment.

The results were gratifying. In almost one-half of the patients the leucorrhea disappeared entirely, many of the women volunteering the information. In another one-fourth of the patients there was marked subjective improvement. The remaining few did not feel that they had been helped much. The objective evidence was even better. In all but one patient the cervix appeared healthier, usually completely cleared of erosion. Five of the women returned to the prenatal clinic with a subsequent pregnancy, and in each the cervix was smooth and healthy, suggesting a certain degree of permanence in the original cure.

The number of cases is too small to form a true statistical study, but the following comparisons were made:

1. The length of labor, as measured by averages, was about the same in the two groups. The figures were: Primiparas, treated, 16.0 hours (±5.1); controls, 17.8 hours (±5.5); multiparas, treated, 11.4 hours (±3.6); controls, 9.0 hours (±3.6).

2. Operative deliveries were proportionately fewer in the treated patients, numbering 2 out of the 46, and 15 of the 140 controls. The only cesarean section was in a control case, elective, for sterilization because of rheumatic heart disease.

3. The morbidity was about the same in both groups. Using the American College of Surgeons criteria, 4 of the 46 treated patients had significant fever (8.7 per cent) and 12 of the 140 controls (8.6 per cent). The only death was in the control group, a post-partum eclampsia following premature delivery.

SUMMARY

1. Cervicitis and its attendant leucorrhea are a real problem in pregnancy, because of the greater discomfort and because of the traditional fear of premature labor if any therapeutic measure, even a douche is used.

2. The absence of evidence in the literature suggests that the dangers of treating the gravid cervix are exaggerated.

3. In the experiment reported, the actual cautery was used to cure the nongonorrheal cervicitis of 48 women between the twentieth and thirtieth weeks of pregnancy. The results, both subjectively and objectively, were good.

4. There was no premature induction of labor, and comparison with 140 controls revealed no significant change in the length of labor, the incidence of operative delivery, or the morbidity. Since the cauterizations were done on the diseased cervix and the control cases were relatively healthy, these data seem to be favorable for the treated cases.

5. While the actual cautery is not to be recommended routinely or to untrained individuals, it appears that cervicitis during pregnancy may be treated successfully and safely.

Appreciation is expressed to Dr. Carl A. Wilzbach, Health Commissioner, Dr. F. Kirby Harder, Assistant Health Commissioner, and Dr. H. L. Woodward, director of the Obstetrical Service of the Cincinnati General Hospital, for their cooperation.

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ECTOPIC PREGNANCY COMPLICATED BY UTERINE FIBROID

RICHARD MANDELBAUM, M.D., YONKERS, NEW YORK

NOTWITHSTANDING years of research, no definite single reason may yet be given for the abnormal implantations in the tubes of ova. Changes in the anatomy and physiology of the tube or of the ovum, acute and chronic salpingitis, present or previous inflammations, swellings of the tubal mucosa, and obstruction by tumor growths have been presented as possible, perhaps probable, factors.

Operation in the early stages of ectopic pregnancy frequently reveals no evidence of previous inflammation. Here other factors are to be considered, perhaps related to the ovum or to some other impediment to its normal passage. In this connection tumors have often been regarded as favoring the development of ectopic gestation. In the present case, a large fibroid offered a real obstacle to the ovum, and caused its probable nidation in the tube.

Mrs. E. R., aged 37 years, complained of abnormal bleeding over a period of eight weeks. She had been well throughout her life, had had a normal menstrual history from the age of 13, had been married at 22, and had had one child three years later. Her menstrual periods had been regular and of five days' duration until eight weeks before her appearance at my office. At that time she had begun to menstruate and the flow had continued for almost three weeks, with interruptions. No pain or discomfort had been associated with the bleeding. For a week she had been symptom free, and then the bleeding had been resumed, continuing intermittently until she reported for examination.

The patient was a well-developed woman, 5 feet 6 inches tall and weighing 122 pounds. Temperature and pulse rate were normal. The only significant finding was a large tumor of the uterus which almost completely filled the lower pelvis. The ovaries and tubes could not be palpated because of the size of the growth. The mucosa of the cervix and vagina was clear, colposcopy showed no sign of malignancy. There was a slight bloody flow from the cervix.

The tumor appeared to be a typical fibroid. This, in itself, could account for the bleeding, although it was puzzling to understand how so large a growth (Fig. 1) could have developed without producing symptoms at an earlier stage.

Operation was indicated, but the patient was very much opposed to such a procedure. She was therefore instructed to wait for two weeks and report for a check-up if the bleeding continued. However, after only one week had passed, the patient was forced to go to bed with severe pain. She had lifted some object in the course of her household tasks and had felt a sharp pain in the left lower abdomen. After one-half hour the pains had slightly diminished, but the abdomen in the region corresponding to the location of the left tube and ovary was tense and very sensitive.

The first impression was that torsion of the left ovary (perhaps cystic) had occurred, although the ovary could not be palpated because of the size of the fibroid. There was no vomiting; the pulse was 82, the temperature 98.8° F., and the urine normal. Urination was painless, but there was some pain after defecation. The blood count was close to normal. (Red blood count 3,900,000, white blood count 8,700, with 80 per cent polymorphonuclears, 18 per cent lymphocytes, 1 per cent eosinophiles, and 1 per cent mononuclears.) The hemoglobin was 80 per cent, and the sedimentation time, normal. Blood pressure was 130/115.

The pain had decreased somewhat and the patient was still strongly opposed to operation, so that twenty-four hours of watchful waiting were decided upon. However, no improvement occurred and the patient finally consented to surgical intervention.

Under general anesthesia, the abdomen was opened, and 100 c.c. of free blood observed in the abdominal cavity. It was obvious that we were dealing with an ectopic pregnancy as well as with a fibroid of the uterus. The tumor was difficult

to dislodge as it was deeply enveloped with the lower part of the cervix and of the corpus. The right tube and ovary were normal and were left untouched. The left tube was a sausage-shaped mass with a blood clot passing through the fimbriated extremity (a tubal abortion). The tube had not ruptured. Hysterectomy and left salpingo-oophorectomy were done (Fig. 1).

Convalescence was uneventful and the patient was discharged from the hospital on the tenth postoperative day.

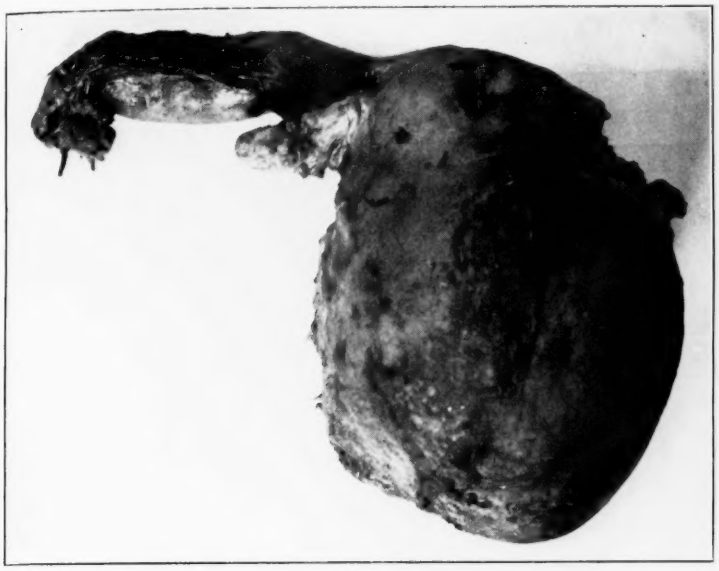

Fig. 1.

COMMENT

This was a clear case of tubal abortion plus fibroid. Probably the tumor had so elongated and compressed the cervix and corpus of the uterus that the ovum was prevented from undergoing proper implantation.

There was little danger of fatal hemorrhage in this case since no tubal rupture had occurred, but merely a tubal abortion with rupture of the inner capsule. This could probably have healed spontaneously. Such old hematoceles are often found years later at operations for adnexal tumors or even at appendectomies.

There was no reason to suspect before operation that an ectopic pregnancy was present, since the patient had not missed a period and the abnormal bleeding could be amply accounted for by the fibroid.

11 Livingston Avenue

ACTINOMYCOSIS OF THE INTERNAL FEMALE GENITALIA

With Report of Case

Earl L. Hall, M.D., Ann Arbor, Mich.

(From the Department of Obstetrics and Gynecology, University of Michigan)

ACTINOMYCOSIS of the internal female genitalia is a rare disease. Up until 1934, when Cornell reviewed the world literature, only 71 cases had been recorded. Since then several cases have been reported both in this country and abroad, but the number on record is still small.

Actinomycosis may be defined as a chronic infection caused by the *actinomyces bovis*, or ray fungus, and is characterized by the formation of multiple abscesses which discharge an exudate containing colonies of characteristic yellow granules.

We wish to report another case of actinomycosis of the pelvic organs.

Mrs. I. W., age 54 years, was first seen at the University Hospital in January, 1938, at which time she stated that she had always been in excellent health until after her third pregnancy, following which she developed symptoms of relaxation of the pelvic floor and prolapse. At this time she was also found to have a mild diabetes mellitus. She had passed through the menopause at the age of 52, two years before admittance.

In the fall of 1936 the patient first began complaining of abdominal pain, located chiefly in the lower right quadrant. In November of 1936 she had an acute attack of pain which was diagnosed as "appendicitis." This subsided under conservative therapy, but the lower abdominal pain and discomfort persisted. In the spring of 1937 her diabetes required insulin. Shortly after this she developed a vaginal discharge which she was told was due to an infection in her tubes. Later in 1937 all of her abdominal discomfort increased, the discharge became worse, the appetite decreased, and she lost 10 or 15 pounds in weight. At this time she revealed a daily febrile reaction up to 100° F., which continued until her admittance to the University Hospital in January, 1938.

Examination at the time of admittance showed a relaxation of the pelvic floor with a second degree prolapse. The uterus was slightly enlarged and limited in mobility. There was definite thickening and induration in the posterior cul-de-sac and in the left adnexal region, with a sensation of an indefinite mass in this area. It was felt she had either a pelvic neoplasm or more likely an extensive chronic pelvic inflammatory process.

After a period of study the patient was sent home to rest and carry on conservative treatment in the form of prolonged hot douches. She returned to the hospital again in March, 1938, stating that all of her symptoms had persisted and that her diabetes had been very difficult to control. Laparotomy was advised and performed on March 27, 1938. The uterus and adnexa were firmly bound down in a mass of adhesions. A bilateral salpingo-oophorectomy and subtotal hysterectomy were done with wide removal of the inflammatory process. On examination of the specimen, the uterine wall was found to be greatly thickened and replaced in areas by soft, necrotic, gray and yellow tissue, the whole mass exuding pus on pressure. Microscopic examination of the tissue revealed an extensive actinomycotic infection of all tissue, a severe purulent inflammation throughout and sinus tracts and abscesses containing numerous colonies of actinomycetes.

Postoperatively the patient did well with no further treatment. After removal of the abdominal drain the wound continued to discharge a moderate amount of purulent material which showed no actinomyces. The wound infection appeared to be superficial with no sinuses, and had almost entirely closed up at the time of her discharge home. The patient was afebrile for several days before her release from the hospital, and her diabetes was now easily controlled.

In general, the prognosis in pelvic actinomycosis appears to be very bad. Doubtless this is partly due to the fact that most patients are far advanced before treat-

ment is undertaken. If this disease is borne in mind, some of the long standing, peculiar, pelvic inflammatory processes may come to surgery sufficiently early to permit adequate removal of the diseased tissues. As postoperative therapy, x-ray and iodides may be used or perhaps thymol. Under such management the ultimate prognosis may be improved.

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PRECOCIOUS MENSTRUATION

Henry S. Fischer, B.S., M.D., F.A.C.S., Brooklyn, N. Y.

(From the Gynecological Service of Beth Moses Hospital)

DUE to the increased interest in the physiology and pathology of menstruation, the following case report is submitted:

R. A. (No. 87853), white, Catholic, full-term child born Nov. 22, 1934, present weight 47 pounds, and 42½ inches in height, was admitted to the Pediatric Service of Beth Moses Hospital, on April 21, 1939, with a history that her mother had noted an increased prominence of the child's breasts, nipples, and "private parts." In addition, the child had first menstruated in July, 1938, at the age of 3 years and 8 months for two days, and about every three months thereafter for two to three days. Her last menstrual period occurred during her present preoperative stay in the hospital.

The patient has one sister 6 years of age who is considered normal in every respect. Both parents were born in the United States.

Her mother's menstrual history began at the age of 15, occurring every three months, lasting for three days. However, within the past few years she has maintained a normal menstrual cycle, in that her periods have been occurring regularly every thirty days. The mother is one of 15 children, 8 sisters and 5 brothers all living and well. One brother and one sister had died of unknown causes. There was no history of any abnormality in the menstrual cycles of her 8 sisters. There was no family history of tuberculosis, cancer, or diabetes.

Mentally, the patient appeared normal for one of her own age, but physical appearance gave one the impression of observing an older individual. She was well developed, and upon physical examination was essentially negative except for markedly well-developed breasts and nipples, and markedly hypertrophied labia majora and minora. No pubic or axillary hair was noted. There were no evidences of undue muscular development or virilism.

Abdominal examination was essentially negative except for a slight fullness which was noted in the left lower quadrant. However, no tenderness, rigidity or definite masses were noted. Rectal examination revealed the presence of a freely movable mass about the size of a small plum, lying in the posterior cul-de-sac and to the left.

Ten days after admission, the patient was transferred to the Gynecological Service for further observation, study and treatment. Blood and urine were normal.

The Friedman test was negative, basal metabolic rate, plus 28 per cent, and vaginal smears were negative for gram-negative intracellular diplococcus.

X-ray studies of the abdomen showed gas presence in the colon up to splenic flexure and not below, possibly an indirect evidence of some soft tumefaction, pressing on the gut but not of sufficient density to contrast with the surrounding soft

structures. Further x-rays showed premature appearance of the epiphyses for the scaphoid, trapezoid, and pesiform; of the middle and proximal rows of the phalanges; of the lower end of the radius and ulna; and unduly developed skull with heavy well-developed sella turcica.

The spine showed excellent development of bone. The impression was one of premature osseous development throughout.

Pregnanediol determinations (Drs. Kantrowitz and Kahn) upon urine collected preoperatively, gave results comparable to those occurring in the early months of pregnancy (31 mg. of pregnanediol glucuronate).

With a preoperative diagnosis of a precocious menstruation etiologically caused by a possible granulosa cell tumor of the left ovary, the patient was laparotomized under open drop ether anesthesia on May 6, 1939 with the following findings: The uterus was regular, slightly enlarged, and of unusually soft consistency. The left

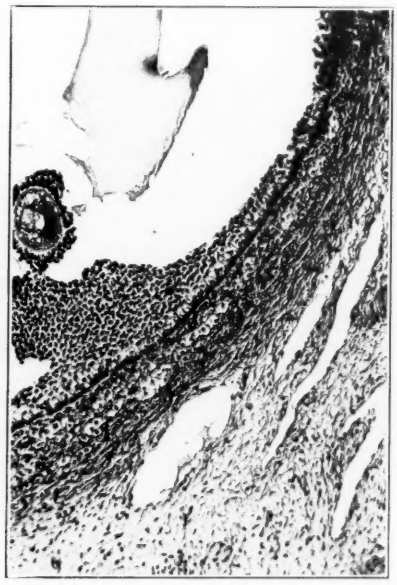

Fig. 1.

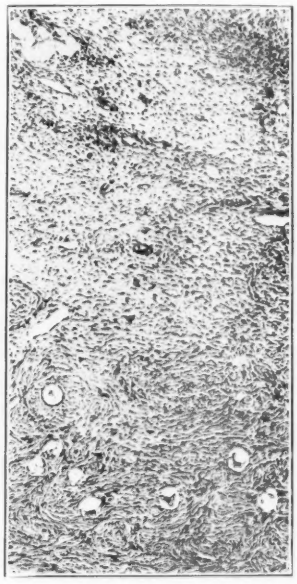

Fig. 2.

Fig. 1.—Graafian follicle with cumulus.
Fig. 2.—Ovary with primordial follicles.

ovary was about the size of a small plum and in appearance resembled an adult microcystic ovary. The right ovary was normal in size and appearance, solid and not cystic with a thick tunica and was about ⅙ the size of the left ovary. The tubes were grossly normal. No other abdominal masses were palpable.

Pathologic Report.—(No. 8821.) (Dr. A. Kantrowitz.)

Gross: Specimen consisted of left ovary, measuring 3.5 by 3 by 1.5 cm. and weighing 8 gm. A cystic mass, 1.2 cm. in diameter, was adherent to the midpoint of one surface of the ovary. The ovary was boggy in consistency and presented a mottled yellow and gray color with translucent areas presenting themselves beneath the capsule. The surface was smooth. Cross section revealed the presence of a considerable number of cystic areas, ranging in size from less than 0.2 cm. in diameter to a cyst measuring 1.5 cm. in diameter. All of the cysts contained clear, straw-colored fluid. The wall of the largest cyst presented a bright yellow color.

Microscopic: (Figs. 1 and 2.) The ovary contained no neoplasm.

There were ova in all stages of development from the primordial follicle to the mature Graafian follicle with luteinization of the theca interna. The large cyst falls into the latter category. Atretic follicles were also noted.

Diagnosis.—(1) Ovary, as in puberty; (2) Graafian follicle.

The postoperative course was entirely uneventful, with the wound healing by primary union, except for the fact that as patient was about to be discharged on the fourteenth postoperative day she developed the prodromal signs and symptoms of measles necessitating her removal to the Kingston Avenue Hospital for Contagious Diseases.

Repeated follow-up examinations at about monthly intervals, have shown no very marked recession in either breasts, nipples, or vulva. Up to the time of submission of this report, approximately five months postoperatively, no further vaginal bleeding has been noted.

DISCUSSION AND SUMMARY

In this country with 13.9 years as the average age of onset of the menses, menstrual periods occurring and recurring regularly below the age of 9 and accompanied by some evidence of precocious maturity such as increased prominence of breasts, hair on pubis or vulva and premature skeletal development, may be definitely classified as cases of precocious menstruation.

Etiologically, one can only state that precocious puberty, like the normal process, is probably due to a stimulus arising in some way from the ductless gland chain, and especially from the generative glands. In the numerous reports of the syndrome of sexual precocity reported in the literature, the condition is ascribed by most authors to disturbances of either the pituitary body, ovaries, adrenals, or the pineal gland. Elterich[1] analyzing 25 cases of precocious menstruation upon whom autopsies or operations were performed, observed that in 21 of these, tumors or cysts of the ovaries were found, the majority of these tumors being sarcomas. However, neoplasms other than the granulosa cell tumors, may be the cause of sexual precocity.

Evaluating all of our presently available clinical, laboratory, and pathologic data, we do not look forward to noting a regression or recession of symptoms above described but prefer to assign this case to the first and major of the three groups described by Lenz[2] who collected and analyzed 130 such cases, to wit: a case of premature menstruation with evidences of general body development which characterize puberty, and not associated with any tumor involving the pineal, pituitary, ovarian or other ductless glands.

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789 St. Marks Avenue

FETAL DEATH DUE TO TOXEMIA OF THE MOTHER

A. T. Lundgren, M.D., and William A. Boice, M.D., Chicago, Ill.
(From the Augustana Hospital)

IN MANY statistical reports, listing the causes of deaths of the newborn, it is stated that toxic conditions of the mother are responsible. The literature contains no definite reports of the exact nature of this effect on the baby. We are reporting the following case because it illustrates one result of severe toxemia in the mother.

The mother, G. L., a 34-year-old white primipara, was admitted to the Augustana Hospital Dec. 20, 1938, at term. The prenatal course was essentially negative, except for a moderate amount of nausea and vomiting during the first two months of gestation. The blood pressure and urine had remained within normal limits. She had been having labor pains for approximately twenty-four hours before notifying us of her condition. On admission to the hospital she was having strong pains every three minutes. The head was in the pelvic brim and the cervix dilated about 4 cm. The temperature on admission was 98.8° F. Four hours later it was 100.2° F. and continued to rise until it reached 102.2° F., eight hours after admission. Her condition remained the same during her first twenty-four hours in the hospital. She

was given two infusions of 10 per cent glucose in saline, 1,000 c.c. each. During this twenty-four-hour period, the head had advanced a little and the dilatation of the cervix was between 6 and 8 cm. The patient was surgically prepared, and under complete ether anesthesia Dührssen's incisions were made in the cervix and the baby was delivered by midforceps extraction. The baby cried spontaneously. Fourteen hours after delivery the baby had a cyanotic spell which was relieved by the removal of mucus from the throat. The following day he seemed listless at times, but he appeared to be progressing satisfactorily until the morning of the seventh day when he became very cyanotic. He was placed in an incubator and given oxygen inhalations and 2 per cent glucose solution subcutaneously. He received 40 c.c. of whole blood intramuscularly. He appeared to improve for a few hours, but again became cyanotic and died eleven hours after the first cyanotic attack.

The mother continued to have fever for seven days. She received 40 gr. of acosulfamid daily during this febrile period and 5 gr. three times a day for several days after her temperature became normal. No satisfactory explanation can be offered for the continued elevation of temperature post partum. Occasional pus cells were found in the urine at two examinations, but her condition could not be traced to this. Agglutination tests were negative. The patient had no specific complaints and did not know that her temperature was elevated until she was given this explanation for her removal from the obstetric floor. She was discharged in good condition after eighteen days in the hospital.

An autopsy was performed on the baby and the following significant findings were present:

The heart weighed 18 gm. The right auricle was markedly dilated. The epicardium was smooth and glistening and the site of occasional pin point-sized bright red markings. The myocardium was rather pale, grayish red in color. The mural endocardium was smooth and glistening; the mitral, aortic and pulmonic leaflets were thin and pliable; the tricuspid leaflets at their free margin were the site of rather indistinct and glistening excrescences not exceeding a millimeter in their maximal diameter. The ductus arteriosus was patent, thick walled, and the lining surface was wrinkled. The foramen ovale was patent, but covered with a delicate, transparent, gray membrane, which was incompletely attached to its margins.

The left lung was mottled grayish red to dark red in color and noncrepitant. The pleural surface was smooth and glistening and the cut surface was rather dark grayish red. At the lower border of the upper lobe was an 8 by 10 mm. sized area darker red than the surrounding lung and sharply demarcated on its cut surface. The right lung was smooth, glistening, and pale grayish red, except for a dorsal aspect, where it was darker red in color.

The liver weighed 100 gm. The capsule was smooth and glistening and delicately mottled dark red to purplish red and speckled with pin point, sharply circumscribed gray areas. The cut surface of the liver had a distinctly brownish cast to its dark red color and was densely speckled with pin point-sized gray to grayish tan markings.

The spleen weighed 12 gm. It was smooth, dark red, and firm. The cut surface was dark red, the markings were rather poorly defined, though here and there pin point gray markings could be distinguished.

The capsules of the kidneys stripped readily; the usual fetal lobulations were present. The surface was smooth and glistening and light red to grayish tan, with occasional bright red pin point markings. On the cut surface the cortex averaged a millimeter in thickness, the medulla was clearly demarcated, the cortical markings were rather poorly defined, the pelvis was pearly gray.

The adrenals were firm and light yellowish gray in color, heavily speckled with irregular pin point to pinhead-sized dark red markings. On the cut surface the adrenal cortex was of moderate thickness, pale yellowish gray, and speckled irregularly with dark red markings.

Microscopic Findings.—Heart: The muscle fibers of the myocardium of the left ventricle were well preserved; the blood vessels were not remarkable. The myocardium of the auricle was rather poorly developed and the fibrous stroma was rather edematous. The mural endocardium displayed a moderate subendocardial edema. The valve leaflets on their auricular surface were rather irregular and thrown up into low humps as a result of a rather marked interstitial edema, which achieved

its maximum at the free end of the leaflet, where the outline was irregular and the leaflet was markedly thickened. The vascular spaces could be identified in the leaflet, as is normal in this age group. A bit of mediastinal fat displayed a rather extensive area in which the red cells had been extravasated and the tissues were necrotic, and there was a scattered infiltration of polymorphonuclear leucocytes and occasional lymphocytes.

Liver: The normal architecture of the liver was markedly distorted. The liver cells were enlarged and often confluent areas were present as mere necrotic shells or replaced by pink-stained granular debris and nuclear debris. The sinuses in these areas were distended with red cells or the remains of blood cells, and the cellular structure was lost. Irregularly arranged about the margins of these areas, more or less well-preserved liver cells, grading through cells in various stages of degeneration into necrotic areas, were seen. In instances these parenchymal cells were of moderate size, with finely granular cytoplasm. In many instances there was more or less marked fine to coarse vacuolation or coarse granulation of the cytoplasm. The nuclei varied in their staining qualities, and a rather considerable amount of coarse brown granular pigment was deposited in the cells. The distortion of the necrosis was irregular, but in the main it appeared to be more pronounced about the portal spaces, while the better preserved liver cells tended to be distended about the central veins, giving the necrosis roughly a marginal or periportal distortion. The section was almost entirely devoid of leucocytic infiltration.

Kidney: Immediately under the cortex an occasional extravasation of blood was seen. Elsewhere the glomeruli were rather small, the cells were compactly arranged and deeply stained, as is characteristic of this age group. Bowman's space was free of contents. The tubular epithelium displayed a coarsely granular cytoplasm, their cell outlines were swollen, and the free borders of the cells were often ragged. The nuclei were variable in their staining qualities, many were pale, and in numerous instances the nuclei were missing. Granular debris was present rather abundantly in the tubular lumina. The blood vessels were moderately distended with red cells.

CONCLUSION

A case is reported in which the death of the newborn child was the result of a high fever of undetermined origin in the mother. It is of particular interest to note that the effect of this toxemia on the baby was to produce a type of liver destruction similar to that seen in the livers of patients dying of eclampsia.

2155 CLEVELAND AVENUE

SOME OBSERVATIONS REGARDING THE FETAL HEART TONES AND THE PRESENCE OF MECONIUM DURING THE COURSE OF LABOR*

E. L. KING, M.D., NEW ORLEANS, LA.

(From the Department of Obstetrics, Tulane University, School of Medicine)

THE auscultation of the fetal heart during labor is a matter of routine in every well-conducted obstetric case, and the importance of this simple act cannot be overestimated. However, there are a few points which might be mentioned in this connection which I feel may be of interest, especially since I find no mention of these details in obstetric textbooks.

In the first place, I wish to protest against the widely published admonitions to the effect that fetal danger is indicated by a pulse rate over 160 or under 100. In my experience, the upper figure is too low; in many instances I have noted rates of 170 or 180 during labor, with regular rhythms, followed by the deliveries of normal babies, whose resuscitation was not difficult. In one case, the fetal heart

*Presented at a meeting of the New Orleans Gynecological and Obstetrical Society, June 1, 1939.

rate was 180 for six hours; delivery was effected by Dührssen's incisions, midforceps, and episiotomy; the baby was apparently not affected and was easily resuscitated. On the other hand, I am firmly convinced that babies are occasionally lost because of a false sense of security when the heart rate is found to be still over 100, the fact that it is becoming slower or has a tendency to become irregular not being considered significant. I feel that a slowing heart rate is a very grave matter, and that the baby is in danger. Briefly, I believe that a rapid rate means simply threatened or early asphyxia, while a slowing rate, to my mind, signifies increased intracranial pressure, and may presage intracranial hemorrhage.

In most textbooks little or no emphasis is placed on the irregularities that may be noted in the fetal heart tone. These alterations may be noted (a) during the latter part of pregnancy, before labor has begun, or (b) after labor has developed. In the first instance (before labor), marked irregularity may be noted occasionally; this is at times transient, at times rather persistent. Naturally, one thinks that the baby is in danger, and that there must be some interference with the fetal circulation. This may be so, and it is probable that, in case of intrauterine fetal death, cardiac irregularity may precede the death of the fetus; however, I have never observed this phenomenon. I have discovered marked irregularity of the fetal heart several times on routine prenatal examination, with subsequent delivery of an absolutely normal infant. One such instance was noted recently. The irregularity was so marked that the fetal pulse could not be counted. This condition was found on every examination over a period of several weeks; I considered the possibility of a cranial defect, but the x-ray showed a normal skull. After an uneventful labor, a healthy child was delivered, the heart was negative, and the postnatal pulse has been perfectly regular. I can offer no explanation for this state of affairs.

Of considerable importance, of course, is irregularity of the fetal heart during labor. It is essential, however, to consider the time of this irregularity in relation to the uterine contractions. It will be noted frequently during the labor pains, and for a few seconds after the cessation of each pain. The heart rate will then become perfectly regular and of the normal rate. This variation in the rate has no significance. At times, however, there will be an irregularity for about one-third or even one-half the interval, between the pains, then normal rate and rhythm will be resumed. This generally means that the cord is around the neck, and that there is not very much slack, so that there is some tension on this coil during the contraction. If there is plenty of slack, this slowing will not be noted. There is no danger to the child in such circumstances. One can at such times astonish the attendants by predicting that the cord will be found around the neck. On the other hand, if the irregularity persists for the entire period between the uterine contractions, the baby is generally in serious danger and delivery should be expedited if it is possible to do so. If pituitary extract has been administered, and the pains have become unduly strong and the interval is markedly shortened, irregularity of the fetal heart will be noted and signifies fetal distress. Fortunately, the effect of the pituitary extract is usually transient and normal conditions are soon re-established. If not, immediate delivery, if feasible, is indicated; if this is not possible, deep anesthesia to relax the uterus is necessary.

Now, as regards the presence of meconium in the amniotic fluid in vertex presentations, I feel that undue emphasis has been placed upon this occurrence, and that it is not always an indication of fetal distress, as obstetric literature would lead us to believe. This is particularly true if quinine has been given for the purpose of aiding in the induction of labor. But in patients receiving no quinine, we will frequently observe, when the membranes rupture, that the amniotic fluid is stained to a variable extent with meconium. If the heart tones are regular and of the normal rate, and if the pains are not too intense or too frequent, one can wait and let labor progress until delivery can be safely expedited. I do not feel that this development should be ignored entirely, but I am of the opinion that it should not be allowed to hurry us to the extent that difficult forceps extraction or version would be performed. Provided the baby appears to be in good condition, and the labor is progressing satisfactorily, a reasonable period of watchful waiting will usually be found to be the best procedure. Individualization is of prime importance under these circumstances.

My reason for discussing the matter is that these details are not sufficiently clarified in obstetric literature and hence erroneous ideas are implanted, especially in the minds of medical students. I believe that it should be made clear that a rapid heart rate, even 170 or 180, if regular, is not necessarily a cause for great alarm, provided the pains are not unduly strong nor too close together. On the other hand, should one wait for the heart rate to drop to 100 before becoming uneasy, one will frequently deliver a dead or a seriously damaged baby. Furthermore, it should be made plain that the presence of meconium in the amniotic fluid in vertex presentations deserves serious consideration, but that it does not always mean grave danger to the baby, and hence should not of itself cause us to resort to a difficult operative delivery.

THE USE OF ANTISEPTIC OIL IN THE TREATMENT OF VAGINAL AND CERVICAL INFECTIONS*

W. A. Reed, M.D., New Orleans, La.

THE continual and persistent use of oily preparations from the earliest recorded time is indisputable evidence of their value in the treatment of infections. Microscopic studies of various tissues treated with oils show that the thinner vegetable oils are capable of quite considerable penetration into the deeper layers of the skin.[1] This penetration is undoubtedly aided by capillary action when the oil is applied to surfaces rich in glandular structures, such as the cervix uteri.

Judkin[2] in 1917 reported 25 cases of wound infections treated by local applications of liquid petrolatum, with rapid healing and excellent results. He believed that its virtue lay in the fact that the "low specific gravity of the oil allowed it to penetrate into all infected pockets," and that it "further promoted healing by encapsulation of the bacteria."

Recently the use of one of the commercial antiseptic oils has been adopted as the procedure of choice in the care of the skin of newborn infants. It was found to be particularly efficacious in the prevention of bullous impetigo of the newborn, pemphigus neonatorum, and dermatitis exfoliativa neonatorum, the etiology of which is the staphylococcus aureus.

The study reported here deals with the treatment of approximately 150 cases of cervical and vaginal infections of various types. About half of them were gonorrheal in origin, while the remainder were due to *Trichomonas vaginalis*, senile vaginitis, infections resulting from cervical lacerations, simple nonspecific endocervicitis, etc.

After many years of experience with various medications and suppositories, it was decided to experiment with one of the better known commercial antiseptic oils.

The plan of treatment was to first thoroughly irrigate the vagina with some warm antiseptic solution, such as permanganate of potash, and then apply a tampon soaked in the oil directly against the cervix, to be removed by the patient from four to twelve hours later. Antiseptic douches of choice were also used at home once or twice daily. The oil tampons were applied every second day for the first week, then twice a week for the following two or three weeks, and then once each week thereafter.

In cases of *Trichomonas vaginalis*, smears failed to show the organisms after two or three treatments, although in a small number of patients smears again became positive a few months after all treatment was stopped. Whether these were true recurrences or new infections could not be determined.

*The preparation employed is that marketed by the Mennen Company. It includes hydroquinone, hydroxy-quinoline and chlorbutonol, dissolved in sesame oil as a vehicle.

Baby girls infected with gonorrhea were treated by daily instillations of oil into the vagina.

The urethra and bladder in all gonorrheal cases were, of course, treated at the same time by standardized methods of irrigations, injections, dilatations, etc.

Practically every patient also received one of the several preparations of sulfanilamide either by mouth or hypodermatically.

Smears for gonococci became negative after two or three weeks' treatment in almost all cases, although a few remained positive for as long as eight weeks. There was also a definite decrease in the number of other bacteria that normally flourish in the vaginal and cervical secretions.

Profuse discharges stopped promptly, and cervical erosions were covered with healthy epithelium in a comparatively short period of time. In many cases there also seemed to be a definite lowering of the pH of the vaginal secretion with a return to normal acidity.

Patients all seemed to appreciate the immediate soothing effect of the oil as well as the absence of staining that results from the use of various dye preparations.

CONCLUSIONS

The use of antiseptic oil appears to be a valuable adjunct in the treatment of infections of the cervix and vagina.

The above conclusion is based on the treatment of approximately 150 such cases.

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A SAFETY LABOR BED

R. A. Bartholomew, M.D., Atlanta, Ga.
(From the Emory Hospital)

INCREASING use of the amnesic method of relief of pain in labor by the use of drugs which obliterate the memory of events in labor, has necessitated more constant nursing supervision of the patient, to prevent infection from self-contamination of the vulva and injury from accidental rolling off the bed.

Mental excitation under this treatment varies with the temperament of the patient and the drugs used, but in some cases the patient may be very restless, trying to sit up and flinging her arms and legs about in forcible, incoordinate movements. During the pains she may subconsciously try to alleviate her discomfort by pressing her fingers against the vulva and thus infect herself unless restrained by the nurse.

Heretofore, accidental rolling off the bed, has been prevented by fastening boards or rails to the sides of the bed or using the crib type of bed with perpendicular metal sides which can be raised into position.

The objections to this type of bed are that the patient may become apprehensive prior to the induction of amnesia by the implied necessity of restraint and after she has been rendered amnesic, she may bruise her arms or legs by striking them against the metal sides. Furthermore, there is the added objection of the interference with the nursing and medical care of the patient, offered by the perpendicular metal sides.

To overcome these objections, the "trough" type of bed shown in Fig. 1 was devised by me.* It has been used at the Emory Hospital with good results.

On admission to the labor room, the patient is put in what, to her, is an ordinary conventional-appearing bed. When she has reached the stage of labor indicated

*Manufactured by the Comper Manufacturing Company of Pittsfield, Mass.

for induction of amnesia, the head may be raised by the Gatch mechanism (*A*) to facilitate oral administration and retention of the drug. When amnesia has been effected and the patient begins to sleep, the head elevation is lowered and a section, ten inches in width, along the entire length of each side of the bed (*B*) is raised (simultaneously) to an angle of 45 degrees, by downward pressure on the foot pedal (*C*) which can be notched securely in this position.

This creates a trough which effectively prevents the patient's rolling off the bed. Since the mattress slightly overlaps the elevated sides, the patient cannot injure herself, regardless of how violent she may be. The rings (*D*) permit reasonable restraint of the patient's arms near the sides of the bed, by means of padded leather cuffs which not only prevents self-contamination of the vulva, but prevents any coordination of effort to get out of bed. It is impossible for the patient to raise

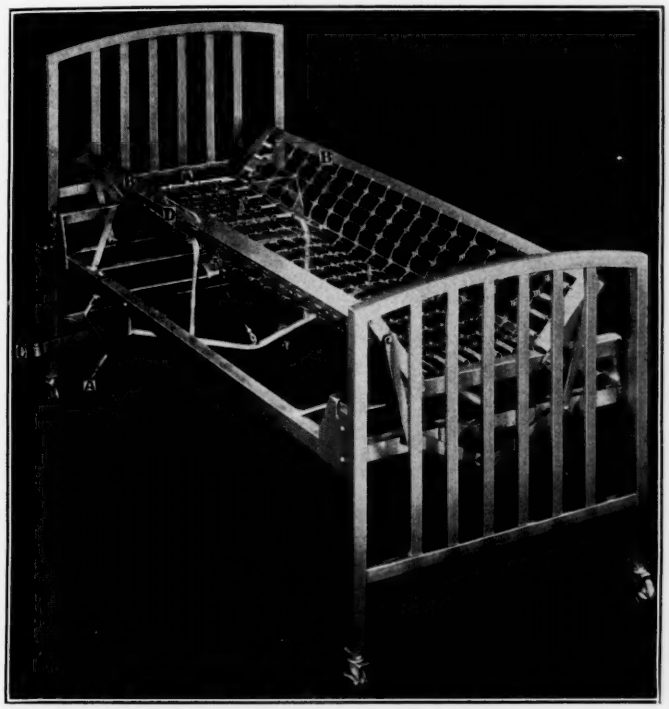

Fig. 1.—Showing bed with sides raised. The latter are flattened out when patient is placed on bed.

her hips over the raised sides. There is no interference with rectal or abdominal examinations or nursing care of the patient. The bed is large enough for obese patients, and, being of standard width, it can be readily moved from one room to another. The nurse is relieved of much physical strain in controlling the patient, and the hospital and the physician are assured that the patient cannot injure herself.

The safety labor bed, while devised primarily for obstetric use in amnesic or eclamptic cases, is of definite value in medical or surgical cases, as in comatose, irrational or postanesthesia cases.

A MEMBRANOUS CAST OF THE UTERUS, TUBES, AND CERVIX

GEORGE A. WILLIAMS, M.D., ATLANTA, GA.
(From the Department of Obstetrics and Gynecology, Emory University School of Medicine)

MEMBRANOUS dysmenorrhea is fortunately not very common, but complete casts of the endometrium are by no means rare. I can find no record, however, of an intact cast of the entire upper tubular tract having been extruded.

A white, married nullipara, aged 27 years, had dysmenorrhea since the onset of menstruation at the age of 13. Periods occurred every twenty-eight days and lasted seven to eight days. Membranous casts were first noticed at the age of 20 and on several occasions intact casts of endometrium were passed.

Fig. 1.—The constriction of the upper fourth of the endometrial portion of the specimen was produced by string used in mounting.

The family history was irrelevant and the personal history disclosed nothing more important than occasional urticaria and angioneurotic edema. General and pelvic examinations disclosed no abnormality.

A specimen passed January 4, 1939, was remarkable in that it consisted of a perfect cast of the mucosa of the Fallopian tubes, uterus, and cervix in one piece (Fig. 1). Microscopic sections of the cast were not made because the patient had preserved it in boric acid solution instead of alcohol. Aspiration biopsy twenty-four hours before onset of a menstrual period revealed normal premenstrual endometrium.

Treatment, including antiallergic regimen, calcium, and many hormone preparations, has been unsuccessful. A dilatation and curettement performed at the time of an emergency appendectomy did not even improve the subsequent period. There has been no change in the menses since marriage eighteen months ago.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

GENERAL SUMMARY OF THE SESSIONS ON OBSTETRICS OF THE FIRST AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY*

GOODRICH C. SCHAUFFLER, M.D., PORTLAND, ORE.

CHARACTERIZING this effort to consolidate the obstetric data offered to the American Congress, it has been remarked that it is indeed difficult to redistill a distillate. Papers presented before these sessions are in the main epitomes. Were it not for the impressive experience and weight of authority which lies behind much that has been presented, a good deal of the material offered to the Congress might be said to be composed of commonplaces. Nearly all of the speakers on this program have quoted at considerable length. Your reviewer submits with absolute candor that in most instances the authors' own statements bear more of the weight of vested authority than those which he has quoted. The effort to select material for this report will of necessity have been dictated chiefly by the reviewer's personal interest more than by any well-advised critique. The result is, of necessity, haphazard—but the intention is definitely to be helpful—especially to those who have heard only a part, or perhaps none, of the proceedings of the Congress.

THE SECOND STAGE OF LABOR

Considerations of the second stage, including dystocia, forceps, breech, and general complications, have been discussed by Harris, Caldwell, Titus, Danforth, Cosgrove, and Rucker. Attention may be called to a statement made by Harris of the University of Wisconsin. He says, "External pelvimetry of the superior strait has its chief value in *classification* of contracted pelves rather than in their *recognition*." This statement should be emphasized as illustrating the trend away from academic architectural considerations of the pelvis toward a functional stereomobile concept of the pelvis in labor. The museum type of pelvic classification is giving way to the working concepts of Caldwell and Moloy, Thoms and others. Qualifying this statement, Harris continues, "In spite of valuable additions to our knowledge of the subject in the past few years, the accurate diagnosis of pelvic contractions has not been freed of its technical difficulty. Of the two methods of pelvic mensuration in common use manual pelvimetry is the oldest, most widely used and perhaps the most valuable." He is on the side of the majority of clinicians when he states "many have experienced technical and interpretative difficulties with the roentgenographic methods of pelvimetry, which for the present,

*This paper was presented in extended form before the General Sessions of the American Congress on Obstetrics and Gynecology at Cleveland, Ohio, September 11 to 15, 1939. From this report gynecologic subjects have been omitted as have papers to be published in this JOURNAL and one or two manuscripts not made available to the reviewer.

I believe, limit their value.'' Concluding, he states, ''Careful pelvimetry, the use of the impression method . . . and the study of serial roentgenograms of the bony pelvis and the fetal head in those cases in which the head fails to engage as term is approached, will enable one to more nearly approach that obstetric ideal which is the aim and desire of all.'' Harris states cogently that in the State of Michigan 21 per cent of patients have been delivered without benefit of *any* type of pelvimetry.

Speaking of a swing toward a stereomobile concept as against the museum concept of the pelvis, I wish to signalize the contribution of Caldwell of Columbia University. In agreement with Harris, he avers, ''By the use of stereoroentgenograms disproportion between the head and the pelvis can be seen and a borderline case recognized as such. But in most instances the proper degree of significance which should be attached to this known degree of disproportion cannot be determined usually until after a trial of labor.''

Caldwell, the originator of a new school of dystocic psychology, examines patients by x-ray before, during, after, and in between. He has charted the pelvis usefully, but his charts are replete with figures and characters which are for the present, at least, puzzling to the average clinician who must still navigate by crude reckoning. Caldwell has perfected his equipment, mental and physical, to a point where he seems almost to stand within a pelvis of familiar contours and directs the course of the fetal head by (to him) familiar laws of physics. If Caldwell's contribution to this meeting is perhaps a bit abstruse, it is, on the other hand, a most important one, and not alone to this program, but also to the welfare of the mothers and babies of the future.

Titus' treatise on indications for forceps application and delivery is an epitome. He gives a kindergarten consideration of types of forceps, their functions and contraindications. His presentation of the indications for forceps delivery, quoted from his recent text, may be considered classic. He seems to have found an almost ideal psychologic approach to this much abused obstetric operation.

Titus approves of so-called ''prophylactic forceps operations.'' He says, ''A trained obstetrician may be warranted under ideal hospital working conditions in shortening the time limit for low forceps, previously mentioned as one hour with the head on the perineum without advance.'' Opposing Plass and others, he advocates this procedure with the free use of episiotomy as truly a conservative measure, qualifying his championship by the following statement: ''Forceps delivery of any type can be made a serious operation in the hands of men whose obstetric work is merely a small part of their entire practice, or where conditions are unsuitable for asepsis and good surgical technique.''

Titus does not discard high forceps, but infers that the operation may occasionally be justified (Harris and Danforth to the contrary notwithstanding). He demands that only a trained obstetric operator shall undertake such a procedure and advocates the use of Piper forceps on the aftercoming head. Proof that Danforth's paper is written with teaching intent appears in his argument favoring episiotomy. The mediolateral episiotomy is applauded. The dangers of midline episiotomy are correctly presented. He has never seen the need to use bilateral episiotomy. Relative to so-called ironing of the perineum, Danforth says cogently: ''It is of little importance to the woman whether her levators are separated by the advancing head or by the hand of an overenergetic doctor—the result to her is quite the same.''

Herbert Miller of Yale draws interesting deductions relative to the actual responsibility of cesarean section in fetal mortality rates. Miller is a pediatrician, perhaps more a logician and mathematician, in this particular setting. He presents ''the fallacies in the arguments both for and against operative delivery.'' Miller proves to his certain satisfaction that the *premature* infant birth weight is tremendously important in infant mortality rates in general. Birth weight determines survival. Correcting and recorrecting mortality rates in view of these deductions, Miller finally exonerates cesarean section from actual responsibility in the high fetal mortality rate which accompanies it. Its corrected mortality rate is not more than that of other types of delivery with the exception of breech extraction and

version and extraction. This, however, is not to be interpreted as inferring that cesarean section should replace breech delivery and version and extraction. He leaves us with one conclusion in which his logic is irrefutable: Breech delivery and version and extraction are inimical to low fetal mortality rates.

Rucker of the University of Virginia, in discussing breech presentation, states in a comparison of extended statistics that the gross fetal mortality averages 24 per cent. His own corrected mortality is 7 per cent. The average corrected mortality is 8 per cent. Premature deliveries give a higher percentage of breech presentations. The larger number of prematures among breech deliveries, therefore, increases the death rate.

Rucker agrees with Harris that external version to avoid breech delivery is wise. Bartholomew reduced the incidence of breech deliveries in his clinic to one-half its usual frequency by using external version, which is neither difficult nor dangerous, and safer without anesthesia.

In the conduct of breech delivery, the vital importance of supervision by an experienced, capable and level-headed attendant is paramount. Rucker says cogently, "The first requisite for the successful conduct of breech delivery is a thorough knowledge of the lesions found at autopsy in the babies which do not survive such operations and that haste is to be avoided."

Rucker reserves cesarean section in breech to cases of definite cephalopelvic disproportion, with the occasional exception of an elderly primipara more than ordinarily committed to the concept of a live baby. He prefers the nonoperative and so far as possible, spontaneous breech delivery, facilitated by early and wide episiotomy.

ANALGESIA AND ANESTHESIA

Bartholomew of Atlanta counts mothers fortunate to have at their disposal the many anesthetic agents now available. Pride, of Memphis, found an almost ideal combination of "analgesic, amnesic and anesthetic, in amytal-morphine-scopolamine mixtures." He has had no ill effects on babies in 300 such cases. Bartholomew, is less euphoric; he states that the ideal method is yet to be found. "If by that is meant a method which will cause no restlessness, no excitement, no tendency to uterine inertia, no fetal apnea at birth, and a method invariably successful in producing complete amnesia—it is doubtful whether such a method will ever be found."

Bartholomew arrays the comparative advantages and disadvantages of all available agents. Perhaps because he has recently been using it, he appears to prefer paraldehyde. Bartholomew and Kane are pretty much in agreement. They believe that paraldehyde is one of the safest, if not *the* safest, and they intend to continue its use in spite of its minor disadvantages; namely that low forceps delivery must be routine, with added inhalation anesthesia; restraints are necessary; the taste and smell are obnoxious; rectal irritation, nausea and vomiting are frequent. The babies may be expected to breathe on the average of thirty seconds later than without paraldehyde.

Nembutal, ethylene, and cyclopropane merit further consideration. There is as yet no apparent trend away from morphine. The advocacy of morphine-scopolamine mixtures is not tinctured by sufficient critique. Spinal anesthesia (except for low cervical section) is appropriately ignored. Regional block is not stressed.

PREGNANCY HEMORRHAGE

Calkins of the University of Kansas and Vaux of Philadelphia discuss hemorrhage due to placenta previa. Calkins describes his own experiences. Vaux speaks objectively with the obvious purpose of teaching. The general maternal mortality of placenta previa is given as 10 per cent, the fetal mortality 40 to 50 per cent. Maternal mortality in both conditions is increased in relation to nearness to term and parity. A general tendency to observe the mother's interest primarily, accounts for a high fetal mortality. Observations relative to management cling to tradition: Calkins, candidly appraising his results, believes by hindsight that several babies might have been saved without additional danger to the mother, by cesarean section. Vaux says: "I have given up all attempts at manipulation manually, bag

dilatation or version, in preference to sustaining the individual against blood loss, and instituting prompt and proper operative intervention—first supportive measures, then cesarean."

Calkins suggests rather timorously that even granted a positive diagnosis, it may occasionally, under ideal circumstances, be advantageous to wait in the interests of a more mature baby. By both authors this question is left as it has been in the past, an open one.

The too frequently neglected danger of tragic hemorrhage resulting from vaginal examination is mentioned. Rectal examination should be included in the same warning. Preparations for immediate operative intervention should be completed prior to such examination. Beyond this it is trite but true that the failure to administer blood where it is available, from whatever satisfactory source, leaves the physician open to just criticism.

Litzenberg, Studdiford, Schumann, and Cooke discuss post-partum hemorrhage and the management of the third stage. Litzenberg of the University of Minnesota says that post-partum bleeding following delivery in excess of 500 c.c., is commonly regarded as hemorrhage—that the average justifiable blood loss is 250 c.c. Unfortunately the average blood loss is, actually, he believes, 600 to 700 c.c. Studdiford, of Bellevue, quotes an incidence of pathologic bleeding of 10.5 per cent. Following spontaneous delivery pathologic bleeding occurred in one of each 8 patients. Following midforceps delivery, it occurred in one of each four patients. The incidence of abnormal bleeding, then, seems to parallel difficulty in delivery. The general mortality in post-partum hemorrhage groups is 3.8 per cent. Careful observation of statistics proves that attention to details in management of the third stage can definitely reduce the incidence of serious post-partum bleeding. Factors most often criticized are: efforts to express the placenta prior to its separation; failure to express the placenta once it *is* separated; failure to account for retained placental fragments; failure to discover and repair tears; failure to anticipate hemorrhage in the presence of uterine inertia or a history of former puerperal hemorrhage.

These speakers seem agreed that obstetric pituitary at the end of the first stage is helpful, although Allen, of Chicago, cordially disagrees. They also approve of the use of a reliable ergot preparation intramuscularly following delivery of the placenta. Studdiford noted incarceration of the placenta and increased difficulty in its delivery when ergot was used at the end of the second stage, although Schumann does not regard this possibility seriously. None of these authors puts sufficient emphasis upon the indications for uterine packing, nor is the procedure described. Failure to be prepared to pack and neglect to do so immediately is more frequently and more primarily a cause of death than failure to transfuse.

Manual removal of the placenta is not necessarily to be feared and under the proper auspices and indications, may perhaps wisely be used earlier and more often than it is. In general however, conservatism is advised. Schumann and Cooke underscore the necessity for preparation for hysterectomy, transfusion, or both on the least suspicion of placenta accreta. Schumann knows of four women in whom a placenta accreta was left strictly alone, after packing. All recovered.

Studdiford has discontinued the use of gum acacia solutions because of resultant catastrophes. He voices his suspicion that stored blood does not offer advantages comparable to direct transfusion. The importance of late unexpected post-partum hemorrhage is mentioned and should be stressed. Sudden, unexpected, and severe bleeding after the patient has been returned to her bed should be anticipated and controlled more frequently than it is.

Cooke, of Galveston, discusses unusual hemorrhage in pregnancy. Of hydatidiform mole he says, "In the vast majority of cases the mole may be removed per vaginam without hysterectomy, provided an Aschheim-Zondek or Friedmann test is done every two weeks for about three months, once a month thereafter for a year, and immediately upon the appearance of any abnormal bleeding." The tremendous importance of the application of these special tests to this condition should be signalized. Discussing rupture of the uterus thoughtfully, Krupp avers, "The great majority of cases of rupture at the present time occur as the result of the giving of pituitrin before the cervix is fully dilated or when there is obstruction

to descent of the fetus. Most traumatic ruptures occur from roughly performed forceps operations or versions, especially the latter."

PELVIC INFECTIONS

Goodall, of Montreal, Norris, of the University of Pennsylvania, and B. P. Watson, of Columbia, discuss pelvic infection. Goodall elucidates clearly the various modes of extension, emphasizing the great importance of migration of bacteria via mucous membranes. He is didactic—empiric in spots. For example, he might have some difficulty supporting his statement that "many of these cases (post-partum pelvic infections) are the outcome of trichomoniasis in the puerperal state." Furthermore, others might wish to temper his statement that "the mode of extension can be determined in almost every case, and that when the mode of extension has been determined, the complications which may devolve from each case are predetermined and are fully anticipated." This statement, for many of us, could be made only with reservations. His paper is replete with meaty fragments, some of which cry for further verification. This fundamental treatise on pelvic extension of infection, by the way, is an excellent companion piece to Arthur Curtis' illuminating study of modes of extension of cancer.

Norris epitomizes textbook concepts relative to pelvic infections. His absolute adherence to conservatism versus surgery in the management of these conditions is satisfying. He preaches the gospel of masterly inaction, with the occasional exception of colpotomy or localized drainage. Norris condenses his material so skillfully that he virtually proves that truisms need not be boring.

B. P. Watson, of Columbia, reports helpfully his conclusions from researches on the transmission of puerperal infection. He concludes that in sulfanilamide we have a drug which is almost the specific against this sort of infection and which may prove to be of prophylactic value when general streptococcal infections are prevalent."

COMPLICATIONS OF PREGNANCY

The Thyroid in Pregnancy.—Lawrence Randall of the Mayo Clinic points out tersely and clearly that "the increase in activity of the thyroid gland in pregnancy is not a condition of hyperthyroidism but represents the response of the thyroid gland to the increase in metabolic demands of fetal and maternal tissue." The gland, under normal circumstances, is called upon for hyperfunction. Additional iodine is frequently needed to avert colloid formation. Further, colloid goiter and adenoma in the fetus will be averted by adequate iodine administration to the mother. Attention is called to a group of patients with lowered basal rates without myxedema, particularly in pregnancy. The details of thyroid administration are given, basal rate determinations governing the therapy. The danger of activation of an adenoma spontaneously or by the use of iodine in the pregnant woman is pointed out. The management of active adenoma and Graves' disease in pregnancy is discussed, considerations in general being similar to those outside of pregnancy.

Speaking of *tuberculosis* and *pregnancy,* Jameson, of Saranac, states the case briefly: "The occurrence of pregnancy in a woman with pulmonary tuberculosis is to be avoided if at all possible as it complicates the picture medically, economically and socially. . . . There is ample evidence at the present time, however, to lead us to believe that if the tuberculous woman receives adequate treatment for her pulmonary disease the pregnancy need not give rise to particular worry from a medical standpoint." Jameson points out cogently that whereas much has been done to care for certain classes of tuberculous patients, the pregnant tuberculous woman is woefully neglected. The management of tuberculosis in pregnancy is, ideally, the proper management of both conditions. Abortion for pulmonary tuberculosis is seldom, if ever, justifiable. If it is employed it should never be after the twelfth week. Collapse therapy during pregnancy may be wise. Cesarean section may have an advantageous place in the delivery of the tuberculous woman.

Relative to *heart disease* and *pregnancy,* Jensen, of Washington University, states that "Among the profession as a whole the diagnosis and treatment of heart disease in pregnant women is still very inadequate." He underlines the necessity for

complete cooperation between obstetrician and internist. Of rheumatic heart disease, even in pregnancy, he states: "We no longer consider it steadily and inexorably progressive." He discusses sanely the implications of heart disease in relation to marriage, child bearing, and abortion. He stresses the trend away from abortion under almost any circumstances. He observes that, "The first step in the prenatal care of a woman with cardiac findings is exact diagnosis. . . . By close supervision and energetic treatment of the slightest evidence of failure, most cardiac patients can be carried successfully through term." Jensen also believes that, "A survey of conditions throughout the country indicates that the use of cesarean section for heart disease is finding a sound clinical level." Of hypertensive cardiorenal disease, including eclamptic toxemias, he says, "There is considerable evidence that hypertension during pregnancy is not a fortuitous circumstance but a sign that the patient's cardiovascular renal system is constitutionally inferior and her childbearing life should be governed accordingly."

The surgical, abdominal complications of pregnancy are discussed by Phaneuf of Boston. Fibroids are to be dealt with according to the mechanical necessity but, in general, "pregnancy in a myomatous uterus in the majority of instances evolves without complications and delivery is effected by the ordinary means." A similar generalization will apply to ovarian neoplasms. Retroversion of the uterus may require special management—seldom, if ever, operative. *Appendicitis* in pregnancy constitutes an exceedingly serious problem because of failure of localization on account of the large uterus. During his training the author recalls having seen five women with appendicitis during pregnancy, all of whom died of general peritonitis. The extreme importance of early diagnosis and operation prior to rupture is stressed. Diseases of the biliary tract should, as a rule, yield sufficiently to medical treatment to allow a successful obstetric outcome. Conservative surgical intervention is occasionally indicated. Again, gastric and duodenal ulcer should yield sufficiently to medical treatment. Surgery if absolutely essential should be conservative. For intestinal obstruction, from whatever cause, early surgery is indicated—again conservative. Infected diverticula, ileitis, tumors of the bowel must all be considered. Pregnancy should not deter from employing the known methods of arriving at a diagnosis, including x-rays of the gastrointestinal tract. Resultant termination of the pregnancy is to be managed, if possible, even more conservatively than usual. To avoid this accident, the copious use of narcotics will be advisable. Phaneuf fails to mention the potential value of heavy doses of progestin—the possible value of wheat germ oil.

Pyelitis in Pregnancy.—Traut of the New York Lying-in Hospital points out the reasons for the frequency of lower urinary infections and the serious dangers which they entail. Traut has learned to recognize the very early signs of pyelitis by studying routine pregnancy urine specimens. Ambulatory treatment of patients with suspicious urine, with small doses of sulfanilamide, has markedly reduced the incidence of clinical pyelitis on his service. Special prophylactic attention is given to patients with a history of previous urinary infections. Large doses of sulfanilamide under careful observation are used in serious involvements. Criteria for cure are exacting. Post-partum pyelitis has been almost completely eliminated in his experience by prophylactic doses of sulfanilamide in all suspected patients. Traut offers a convincing and intensely helpful thesis. His observations dovetail neatly with recently published Mayo Clinic studies (Staulker, Schulte) relative to bacteriostasis in postoperative urine retention.

Discussing *endocrine aspects*, Novak, of Baltimore, and George Gray Ward, of New York, adhere to gynecologic applications. In a more general consideration, Allen, of Chicago, agrees with the others that "the indiscriminate use of (these) powerful catalytic agents, often prescribed without even an adequate physical examination for everything from falling hair to normal senility, will not enhance the trust in our profession and will only add to the financial burden of our patients. . . . We are beginning to quote treatment in thousands of units, even in millions. One is reminded of the present financial activities of our government; and the multiplicity of hormones ascribed to the pituitary alone is reminiscent of the A.A.A., N.R.A., or the W.P.A." Allen outlines an extremely useful program for study of the patient. He has a flair for figures of speech. Speaking of endometrial

biopsy, says he, "Our judgment based on these bits of tissue should be tempered by remembering that this handwriting by the ovaries on the wall of the uterus is not as legible or the same in all areas which the curet has explored."

In summary, the reviewer's effort has been to italicize first, recent obstetric developments and improvements now consolidated but not universally employed; second, for re-emphasis, the common abuses of good obstetric practice; third, for reiteration, basic obstetric epigrams. This threefold purpose will have been by no means completely fulfilled. The effort, however, has been to epitomize the important transactions of this Congress for that vast majority of obstetricians who have been unable to attend the sessions of the Congress. For the program itself, certain criticism may perhaps be justly leveled. When, however, the bitter critics of our profession can offer a program so openly devoted to self-critique, so consolidated in the interest of unselfish progress, we may feel more impressed by the bases of their judgment. Another Congress may perhaps achieve improvement in certain respects; but will not be grounded in any finer devotion to an excellent cause.

548 Medical Arts Building

Pearl, Raymond: Fertility and Contraception in New York and Chicago, J. A. M. A. 108: 1385, 1937.

New York and Chicago represent the farthest progression of the process of urbanization in the western hemisphere. This process has produced profound alterations both quantitative and qualitative in human reproduction. Certain aspects of the reproductive histories of 3,951 women dwelling in New York City and 3,589 dwelling in Chicago were analyzed and compared. All the women in both samples were living in wedlock, had been married only once, and were free of any recognized form of gynecologic disease.

The white women of the Chicago sample appear to be somewhat less fertile on the average than the white women of the New York sample, whether measured by pregnancies experienced or live births produced.

Attempted contraception was more frequent among the Chicago than among the New York white women, the percentage of contraceptors being 64 in the former city and 53 in the latter. Contraception as practiced was more effective among the New York women than among the Chicago women.

The data from both cities indicate that women practicing birth control resort to criminal abortion more frequently than do noncontraceptor women. There is reason to believe, and it is expected that later in another place it will be demonstrated, that New York and Chicago are in no wise peculiar in this respect but that the total material of over 30,000 reproductive histories will show the same thing. The abortionist is called on to rectify the inadequacies of birth control.

Grover Liese.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Stilbestrol and Testosterone

Karnaky, K. J.: Clinical Use of the New Synthetic Estrogenic Hormone, Stilbestrol, South. M. J. 32: 813, 1939.

This is a preliminary report upon the use of a synthesized potent estrogenic hormone which is effective when administered orally. Structurally, diethyl-stilbestrol is quite unlike estrone, yet it possesses similar physiologic properties. One milligram is equivalent to 25,000 International Units of estrone when taken by mouth.

Animal experimentation has indicated that it has a low toxicity and a wide margin of safety therapeutically. In a few patients nausea followed its administration, but this was avoided by taking the medication after meals or at bedtime.

It was successfully employed in the treatment of a number of conditions. Excellent results were obtained in the postmenopausal syndrome with considerable subjective and objective improvement; the thin senile vaginal mucosa assumed the characteristics of healthy adult mucosa, and the hydrogen ion concentration changed from alkaline to normal acid reaction following a course of therapy. The claim is made that stilbestrol is 90 to 95 per cent effective in the treatment of functional bleeding. Endometrial biopsies revealed anatomic improvement within forty-eight to seventy-two hours. The prescribed dose was 0.1 mg., two to three times daily, or the entire amount at bedtime. Gonorrheal vaginitis responded well. Oral administration of this hormone is particularly suitable and convenient in the treatment of gonorrheal vaginitis of children.

ARNOLD GOLDBERGER.

Bishop, P. M. F., Boycott, M., and Zuckerman, S.: The Estrogenic Properties of Stilbestrol (Diethyl-Stilbestrol), Lancet 1: 5, 1939.

In recent years attention has been directed toward the estrogenic activity of synthetic compounds which may or may not in common with the naturally occurring estrogens contain the phenanthrene ring. A compound containing 2 benzine rings (diethyl-stilbestrol) was described by Dodds and his co-workers in 1938 and found to compare favorably biologically with the natural estrogens and to be active by mouth. It was administered to 18 patients with amenorrhea of variable duration and resulted in estrin withdrawal bleeding in 8 and rhythmic uterine bleeding in 2 additional patients; 6 patients did not respond though they had previously shown withdrawal bleeding following therapy with estradiol benzoate. One patient had shown no response with previous estrogenic therapy and the other failure had not received previous therapy. The total dosages used varied from 4 to 70 mg.

In a group of 25 patients with menopausal symptoms, response was obtained in 17. A dose of 0.1 mg. daily by mouth was sufficient in one case to produce relief of symptoms and a vaginal estrus smear in fourteen days although the improvement was not maintained.

Two patients with dysmenorrhea obtained relief following daily 0.1 mg. tablets during the first half of the cycle.

Biopsy studies of the mammary epithelium were done in one patient who received 280 mg. of the synthetic hormone by mouth. Proliferation and increased activity of the epithelium was found but nothing suggesting any type of malignant change.

Nausea or vomiting was noted in three of 46 patients but did not depend upon the dosage.

Typical proliferation of the endometrium was demonstrated both in the human being and in the monkey. In the spayed rhesus monkey, a single injection of 0.5 mg. of stilbestrol in oil is sufficient to produce vaginal bleeding after an interval of about twelve days.

CARL P. HUBER.

Palmer, A., and Zuckerman, S.: Further Observations on the Similarity of Stilboestrol and Natural Oestrogenic Agents, Lancet **1**: 933, 1939.

Diethyl-stilbestrol has been shown to have the following properties in common with the natural estrogens: (1) It produces estrus in ovariectomized rats and mice by injection; (2) it causes growth of the endometrium in rats, rabbits, and monkeys and activates the sexual skin in the latter; (3) it causes changes in the feathers of capons and in the teats of guinea pigs; (4) it substitutes for the natural estrogens in the treatment of women with symptoms resulting from hypofunction of the ovaries; (5) it interrupts early pregnancy in the rabbit; (6) it inhibits the gonadotropic activity of the anterior pituitary in rats. It differs from the natural estrogens in that it is much more active by mouth.

The authors have shown that stilbestrol will sensitize the endometrium of the spayed monkey to allow for progestational differentiation. They have shown that it is active equally with estrone when applied intravaginally in oil to spayed mice. They were able to produce estrus in spayed mice also by the percutaneous absorption of stilbestrol in oil painted on the neck.

CARL P. HUBER.

Moricard, R., and Saulnier, F.: Comparative Study on the Activity of Diethyl-stilboesterol and Oestradiol Benzoate in Human Therapy, Ann. d'endocrinol. **1**: 215, 1939.

The authors treated 12 patients, 11 of whom had been previously treated with estradiol benzoate or gonadotrophic hormone, with diethyl-stilbestrol, 1.0 mg. per day for ten days, and compared the results.

Eight of the 12 cases were surgical castrates. The authors' cases show that 7 of the 11 patients treated with estradiol or gonadotrophic hormone obtained symptomatic relief, 2 experienced partial relief, while 2 others secured no relief. Diethyl-stilbestrol gave symptomatic relief to 4, partial relief to 3, and no relief to 5 cases. In 2 of the last 5 cases the symptoms were actually made worse. Seven of the 12 patients experienced moderate to severe gastrointestinal disturbances, in fact, it became necessary to discontinue treatment in 3 of the cases because of these upsets.

Two of the surgical castrates had vulvar ovarian grafts which responded moderately to gonadotrophic hormone but in both cases these grafts responded much more rapidly and intensely to the diethyl-stilbestrol treatment.

The authors conclude that estradiol benzoate, in view of its nontoxicity, remains the basis of gynecologic hormonal therapy.

CLAIR E. FOLSOME.

Varangot, J.: Estrogen Activity and Toxicity of Dihydroxy-diphenyl-hexane, Bull. Soc. d'obst. et de gynéc. **28**: 426, 1939.

The author reports his results with a new synthetic preparation of estrin very similar to stilbestrol. The drug was used in 25 women who had menopausal

symptoms and in 10 women in whom it was desired to suppress lactation after labor. All of the menopausal patients were relieved of their symptoms. However, this new drug produces the same disagreeable disturbances as stilbestrol among these women. On the other hand, only one of the ten post-partum patients experienced intolerance of the drug. The author is at a loss to explain why post-partum patients are resistant to the toxic symptoms of this drug.

J. P. GREENHILL.

Campbell, N. R., Dodds, E. C., Lawson, W., and Noble, R. L.: Biological Effects of the Synthetic Estrogen Hexestrol, Lancet 2: 312, 1939.

A synthetic estrogenic substance called hexestrol (4:4'-dihydroxy-y:8-diphenyl-n-hexane) is evaluated in this report from the standpoint of its biologic effects in comparison with stilbestrol and natural estrogens.

It is found to sensitize the uterus of the ovariectomized rabbit to the action of progesterone and to stimulate the nipples and mammary glands. Impregnation in the rat was prevented by oral administration of hexestrol. Reduction of body growth and atrophy of the gonads followed its prolonged use in rats.

Hexestrol and stilbestrol produced approximately equal increases in the weight of the uterus of the immature rat. When assayed by injection into ovariectomized rats, hexestrol was found more active than stilbestrol, and both were two to three times more active than estrone. These two substances showed approximately the same degree of activity when given by mouth and when applied intravaginally.

CARL P. HUBER.

Boling, J. L., and Hamilton, J. B.: The Effect of Synthetic Male Hormone Substance Upon Follicular Growth and Ovulation in the Guinea Pig, Anat. Rec. 73: 1, 1939.

Adequate administration of synthetic male hormone substance, testosterone propionate, suppressed follicular growth and ovulation in 19 guinea pigs during a six- to eighteen-day period of injection. Ovulation was prevented as shown by (1) the lack of behavioral responses characteristic of guinea pig periods of heat and ovulation; (2) the failure of the vagina to open; (3) the atrophic condition of the ovaries as seen upon operative inspection, and (4) microscopic examination of the ovaries which showed (a) average volume and range of the largest active follicle about that of untreated guinea pigs on the fifth to eighth day of a sixteen-day cycle, (b) a large number of atretic follicles, and (c) no new corpora lutea. In 12 other females the continued administration of testosterone propionate prevented ovulation during nine months of injection.

The reproductive cycle and ovulation returned soon after the cessation of androgen injections; the vagina opened eight to thirteen days after the end of 6 to 18 injections in 10 of 11 animals observed thereafter. Some of these guinea pigs were found to be in a period of heat six to ten days after the opening of the vagina and two others were mated with subsequent bearing and rearing of normal offspring. Two more guinea pigs injected continuously for nine months bore and raised offspring when injections were stopped. Ovulation occurred in a shorter time after the cessation of injections than it does in a normal animal following a period of heat.

J. P. GREENHILL.

Geist, Samuel H., Salmon, Udall J., and Gaines, Joseph A.: The Use of Testosterone Propionate in Functional Bleeding, Endocrinology 23: 784, 1938.

Testosterone propionate (in doses of 300 to 1000 mg. per month) inhibits menstruation and arrests the endometrium at the early proliferative phase, preventing the development of progestational changes. Larger doses cause varying degrees of regression of the endometrium to the state of hypoplasia or atrophy. Following the discontinuation of therapy, the inhibitory effects on the endometrium

gradually disappear and normal estrogen and progesterone effects reappear. It is suggested that the regressive changes noted in the endometrium after testosterone propionate administration are the end results of a primary inhibition of the gonadotropic factors of the hypophysis, causing suppression of the ovarian cycle, with consequent cessation of estrogen and progesterone production.

J. THORNWELL WITHERSPOON.

Phelps, Doris, Burch, John C., and Ellison, E. T.: Effect of Long-Term Injections of Testosterone Upon the Guinea-Pig Endometrium, Endocrinology **23**: 458, 1938.

Adult female castrated guinea pigs were injected with 1 mg. of testosterone propionate daily for 26 (2 animals) or 34 (6 animals) days. Endometrial specimens from these animals were compared with similar specimens from adult guinea pigs which had received 2 R.U. of theelin daily for 21 (17 animals) or 30 to 40 (8 animals) days. Endometria from guinea pigs injected with testosterone showed typical Swiss-cheese dilatation of the glands, moderate proliferation of the surface epithelium, mild proliferation of the glandular epithelium and a mild reaction of the stroma. Endometria from guinea pigs injected with theelin showed typical Swiss-cheese dilatation of the glands, marked proliferation of the surface and glandular epithelium and a strong reaction of the stroma. The results indicate that: (a) the response of the guinea pig endometrium to testosterone is qualitatively similar to the response to theelin; (b) theelin and testosterone differ markedly in potency with respect to their effect upon the endometrium; and (c) cystic dilatation of the endometrial glands may result from the application of a stimulus which is, comparatively speaking, extremely weak.

J. T. WITHERSPOON.

Béclère, C.: Testosterone Propionate in the Treatment of Uterine Hemorrhages, Bull. Soc. d'obst. et de gynéc. **27**: 747, 1938.

Béclère reports a series of 14 women who were treated with testosterone propionate for uterine hemorrhages and who were followed from four to six months. The results were highly favorable. Six women were in the premenopausal age between 45 and 55 years of age. They were given moderate doses, usually 25 mg. a month. The results were good in all the cases.

Among seven women who had functional bleeding due to genital infection, there were 5 favorable results and 2 failures. The last case was that of a woman who had bleeding associated with a submucous fibroid. The bleeding ceased following one injection of 25 mg. of testosterone propionate.

J. P. GREENHILL.

Palmer, R., and Moricard, R.: A Case of Submucous Myoma Treated by Testosterone Propionate, Compt. rend. Soc. franç. de gynéc. **8**: 300, 1938.

Previously the authors reported that they could control uterine hemorrhage by the injection of estrin, progesterone, and urinary prolan. They also reported on the use of testosterone in 1936. They now describe a case in which they brought about a cessation of uterine bleeding by means of testosterone propionate but failed to influence the size of a submucous fibroid which was present. They verified the size of the fibroid by repeated hysterograms. The patient had bled profusely for eleven months, both at the time of the menses and during the intervals. She was given 5 mg. of testosterone every second day for three months, a total of 220 mg.

J. P. GREENHILL.

Bravarski, J.: The Use of Testosterone Propionate in Gynecology, Bull. Soc. d'obst. et de gynéc. **28**: 418, 1939.

The author used testosterone propionate in 40 cases of metrorrhagia associated with fibroids of the uterus, and he met with success in 38 cases. The two failures

occurred in women who were nervous after the hypodermics and refused to continue with the treatment. In the 38 successful cases the menses became regular in frequency and amount and the uteri diminished in size. The author is enthusiastic about this form of therapy and believes it should be helpful in cases of virginal bleeding also. He had one such successful case. He believes that testosterone may be used to overcome the disagreeable symptoms which some women have just before the menses.

J. P. GREENHILL.

Mazer, Milton, and Mazer, Charles: The Effect of Prolonged Testosterone Propionate Administration on the Immature and Adult Female Rat, Endocrinology **24**: 175, 1939.

In the immature rat, prolonged administration of testosterone propionate causes a decrease in the weight of the pituitary, adrenals, ovaries, and uterine horns and inhibition of estrus with mucification of the vaginal epithelium. The degree of uterine atrophy is not in proportion to the ovarian atrophy, presumably because the suppression of estrogen production is partly counterbalanced by the direct stimulative effect of testosterone on the uterus. The adult rat reacts similarly with the exception that the pituitary gland shows no significant decrease in weight. The deleterious effect of prolonged testosterone treatment on the ovaries is temporary. Restitution of structure and function occurs within twenty-nine days.

Evidence is drawn from the literature and the experiments described that the duration of treatment is the determining factor in the effect of testosterone on the ovaries; short treatment produces stimulation and prolonged treatment depression. It is considered that the ovarian atrophy here described is secondary to pituitary inhibition.

J. THORNWELL WITHERSPOON.

Desmaret and Mme. Càpitan: The Value of Testosterone Treatment in the Menometrorrhagias and Menopausal Disorders, Presse méd. No. 51, p. 1031, 1939.

In a previous study of testosterone treatment in mastopathy cases, the authors observed that some of these patients, who had an associated hypermenorrhea or menorrhagia, obtained a favorable return to normal menstrual periods. This observation inspired the present study.

After ruling out local and systemic causes of menorrhagia, the authors were able to group the uterine hemorrhage cases into two groups: (1) young women giving a previous history of difficult labors, puerperal hemorrhage, or an earlier abortion which had not been treated by curettement, and (2) menorrhagias appearing in the premenopausal period. The bulk of patients were in the latter group.

In general the treatment used was a series of hypodermic injections of testosterone propionate, each 10 mg., beginning the ninth day after the onset of the menses and every second day thereafter until a usual total dosage of 80 mg. was reached. In the following months it was usually necessary to decrease the dosage considerably, or to even discontinue the drug. The dosage of testosterone given to each patient must be judged by the individual patient's response.

Due to an imbalance of ovarian and hypophyseal secretions, the patients evidence endocrine dysfunction characterized by symptomatic periods of menorrhagia or amenorrhea. The authors feel that these fluctuating secretory levels not only affect other endocrine glands but the whole organism including the vegetative nervous system.

For those patients with vasomotor symptoms in the premenopausal period without hemorrhages, the writers recommend a combination of testosterone acetate (5 mg.), and one ampoule of gynestryl, three times a month, on every tenth day. Should the menses last longer than ten days, in periods preceding menopause, only a series of testosterone propionate, as previously outlined, is used.

The authors do not mention the number of patients treated with testosterone. They state, however, that the largest group was in the premenopausal period. Five cases are reported in detail. In Case 2 they add an interesting observation that the circumference of the patient's hips, thighs, and knees decreased in size and the patient lost 2 kg. of weight. The writers are enthusiastic about their good results but warn that every patient must have her treatment individualized.

CLAIR E. FOLSOME.

Turpault: The Male Hormone in Women Especially in Cases of Hemorrhage, Gynécologie **38:** 281, 1939.

In the opinion of Turpault male hormones are indicated in women for the following conditions: mastopathies, uterine fibroids, functional uterine bleeding, especially at puberty and at the menopause, intermenstrual pain, uterine hyperplasia, hypertrophy of the cervix, and disturbances of the menopause. He cautions, however, that in addition to the favorable effects of the male hormone there are certain inconveniences. These are as follows: fatigue, which may be overcome by adrenal therapy, excitement, liver disturbances, deepening of the voice, and enlargement of the clitoris.

The dose of male hormone varies with the indications for its use. However, it is best to begin with small doses, such as 5 mg. For mastopathies, from 5 to 30 mg. should be given each month, distributed in from 1 to 5 doses, beginning the tenth day after the onset of the menses. For functional uterine bleeding, as much as 50 to 60 mg. must usually be given each month. For fibroids of the uterus very large doses, from 50 to 500 mg., must be administered.

Not infrequently after the hormone is stopped, the symptoms reappear. In such cases one may try implantation of testosterone in the form of crystals in the skin, as suggested by Parkes.

J. P. GREENHILL.

Moricard, R., and Saulnier, F.: Artificial Development of the Genital Apparatus by Means of the Esters of Testosterone, Gynécologie **38:** 272, 1939.

These authors were able to produce a marked development of the genital apparatus in human beings by means of the synthetic esters of testosterone. This could be accomplished with 100 mg. administered over a period of a month and a half. When 400 mg. were given, there was an almost constant appearance of signs of puberty in children, who had the adiposogenital syndrome. Among women the injection of the esters of testosterone resulted in a disappearance of the neurovegetative symptoms of castration. Likewise this substance was capable of stopping functional uterine bleeding.

J. P. GREENHILL.

Mascio, Aquino: The Action of Testosterone in Functional Uterine Haemorrhage, Folia demograph-gynaec. **36:** 165, 1939.

The author considers the mechanism of the therapeutic action of testosterone and reports results in several cases of functional uterine bleeding. With the doses employed by him (5 to 10 mg. on alternate days) no untoward effects were observed. He found a constant and favorable action in controlling functional uterine bleeding both in puberty and in the preclimacteric.

MARIO A. CASTALLO.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board at the Atlantic City Hospital, Atlantic City, N. J., from Friday, June 7, through Monday, June 10, 1940, prior to the opening of the annual meeting of the American Medical Association in New York City on Wednesday, June 12, 1940. Candidates are requested to note that the dates of the examinations have been advanced one day from those previously announced.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

"The Foundation Prize" of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons

The award known as "The Foundation Prize" shall consist of $150.00. Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

Manuscripts must be presented under a nom-de-plume, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the nom-de-plume and containing a card showing the name and address of the contestant.

Manuscripts must be limited to 5,000 words, and must be typewritten in double spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis. Submit 3 copies of thesis and illustrations to secretary. The successful thesis shall become the property of the Association, but this provision shall in no way interfere with publication of the communication in the journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors. All manuscripts entered in a given year must be in the hands of the Secretary before June 1.

The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

The President of the Association shall annually appoint a Committee on Award, which, under its own regulations, shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting.

JAS. R. BLOSS, M.D., Secretary.
418 Eleventh Street, Huntington, W. Va.

Attention is called to an important announcement on Advertising Pages 13 and 14.